THE INVESTIGATION OF THE PRIMARY RESPONSE OF THE FLASH VISUAL EVOKED RESPONSE

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The topographical distribution of the early components of the flash visual evoked response (VER) were investigated using a twenty channel brain mapping system. Thirty subjects, ranging in age from 21-84 years, had flash VERs recorded using the standard 10-20 electrode system to a balanced non-cephalic reference. The subjects were divided into three age groups a young group, a middle group and an older group. The P2 component (positive component around 100-120 msec) of the flash VER was recorded consistently over the occipital region throughout the age range, as was a frontal negative component (N120) of about the same latency. Only the young age group had this single negative component on the frontal channels, whilst the middle age group showed an additional negative component at around 75 msec (N75). Neither group had a recordable P1 component (positive component around 60-75 msec) over the occipital region. The older age group showed both P1 and P2 components over the occipital region with the distribution of the P1 component being more widespread anteriorly. The frontal channels showed both the negative N75 and the later N120 components.

The frontal negative components were shown not to be related to the electroretinogram or the balanced non-cephalic reference, but were affected by the type of stimulation. Responses recorded to both pattern reversal and onset/offset stimulation did not show the frontal negative potentials seen with flash stimulation.

It was shown that the P1 component is more readily recordable in the elderly and is preceded during middle age by the development of a frontal negative component at around the same latency. The changing morphology of the negative activity in the frontal region across the age range suggests that the use of an Fz reference would produce an artificial P1 component in the middle age group and an enhancement of this component in the elderly, as well as enhance the P2 component in all ages.

Key Words:- visual evoked response, flash, aging, brain-mapping, primary components.

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CONTENTS Page

SUMMARY		2
ACKNOWLEDGMENTS		3
LIST OF FIGURES		8
LIST OF TABLES		13
CHAPTER 1.	INTRODUCTION	15
CHAPTER 2.	THE ANATOMY AND PHYSIOLOGY OF VISUAL SYSTEM	18
2.1.0	The anatomy of the human visual system	18
2.2.0	The physiology of the visual system	23
2.2.1	The retina	23
2.2.1a	The cat retina	23
2.2.1b	The monkey retina	26
2.2.2a	The cat lateral geniculate nucleus	29
2.2.2b	The monkey lateral geniculate nucleus	30
2.2.3	The optic radiation	32
2.2.4	The visual cortex	32
2.2.4a	The cat visual cortex	34
2.2.4b	The monkey striate cortex	36
2.2.5	The monkey parastriate and peristriate cortex	38
2.2.6	Extrageniculate pathways	39
2.2.6a	The extrageniculate pathways in the cat	39
2.2.6b	The extrageniculate pathways of the monkey	40
2.2.7	Summary	40
CHAPTER 3.	THE FLASH VISUAL EVOKED RESPONSE	42
3.1.0	The components of the flash visual evoked response	42
3.2.0	Procedures for recording the flash visual evoked response	46
3.2.1	Electrodes	46

		Page
3.2.2	The reference electrode	49
3.2.3	Amplification	52
3.2.4	Stimulation	53
3.3.0	The effect of age and maturation on the components of the flash VER	55
3.3.1	The effect on the latency of the response	55
3.3.2	The effect on the amplitude of the response	56
3.4.0	The topography of the components of the flash VER	58
3.4.1	An historical review of the mapping of brain activity	58
3.4.2	Topographical investigation of the flash VER by means of scalp electrodes	59
3.4.3	Mapping of visual evoked responses	62
3.4.4	Dipole localization methods	65
3.4.5	Current source density analysis (CSD)	66
3.4.6	Source derivation methods	68
3.4.7	Position emission topographic investigation of evoked potentials	69
3.4.8	Neuromagnetic evoked fields	70
3.5.0	Comparison of scalp and intracortical recordings of the flash VER	71
3.6.0	The clinical uses of the flash VER	73
3.7.0	The flash VER and cortical blindness	80
3.8.0	Summary	83
CHAPTER 4.	THE EFFECT OF RECORDING A FLASH VER THROUGH A CLOSED EYELID	84
4.1.0	Introduction	84
4.2.0	Methods	85
4.2.1	The effect of recording a flash VER through a closed eyelid	85
4.2.2.	The effect of reduced intensity of stimulation on the latency of the flash VER	86
4.2.3	The effect of mental activity on the latency of the flash VER	87

		Page
4.2.4	The light diffusing effect of the eyelid on the latency of the flash VER	87
4.2.5	The effect of different stimulus wavelengths on the latency of the components of the flash VER	87
4.3.0	Results	88
4.3.1	The effect of recording a flash VER through a closed eyelid	88
4.3.2	The effect of reduced stimulus intensity on the latency of the flash VER	93
4.3.3	The effect of attention on the latency of the components of the flash VER	97
4.3.4	The light diffusing effect of the eyelid on the latency of the flash VER	99
4.3.5	The effect of different stimulus wavelengths on the latency of the components of the flash VER	100
4.4.0	Discussion	104
CHAPTER 5.	THE TOPOGRAPHY OF THE P1 COMPONENT OF THE FLASH VER	107
5.1.0	Introduction	107
5.2.0	Methods	108
5.3.0	Results	117
5.3.1	The topography of the flash VER recorded with the eyes open	117
5.3.1a	The P2 component	117
5.3.1b	The P1 component	125
5.3.2	The topography of the flash VER recorded with the eyes closed	131
5.4.0	Discussion	132
5.5.0	Summary	157

		Page
CHAPTER 6.	INVESTIGATION OF THE FRONTAL NEGATIVE COMPONENTS OF THE FLASH VISUAL EVOKED RESPONSE	158
6.1.0	Introduction	158
6.2.0	The ERG and monocular stimulation study	161
6.2.1	Method	161
6.2.2	Results	161
6.3.0	The effect of the BNCR on the recording of the frontal N75 and N120 components of the flash VER	174
6.3.1	Method	174
6.3.2	Results	175
6.4.0	Pattern reversal and pattern onset/offset stimulation	182
6.4.1	Method	182
6.4.2	Results	182
6.5.0	Discussion	187
6.6.0	Summary	195
CHAPTER 7.	DISCUSSION	196
7.1.0	Summary of results	196
7.2.0	Discussion of results	198
7.3.0	The advantages and disadvantages of brain mapping evoked potentials	203
7.4.0	Future work.	204
APPENDIX.	SUPPORTING PUBLICATIONS	206
REFERENCES.		215

LIST OF FIGURES

		Page
Fig. 2.1	The human LGN in coronal section (after Gray 1973)	19
Fig. 2.2	The human visual pathway (after Diamond et al 1985)	21
Fig. 3.1	Figure showing the principles of averaging (after Dawson 1954)	43
Fig. 3.2	The waveform of the flash visual evoked response (after Cigánek 1961)	45
Fig. 3.3	A styalised flash visual evoked response showing the different labelling systems used by various authors. (after Harding 1974)	47
Fig. 3.4	A spatiotemporal map of the VER scalp distribution (after Rémond 1965)	60
Fig. 3.5	An example of a normal pattern reversal and pattern onset/offset VEP (after Wright et al 1985)	74
Fig. 4.1	The group averaged flash VER data of the older age group recorded from the open eye and the closed eye	90
Fig. 4.2	The group averaged flash VER data of the younger age group recorded from the open eye and the closed eye	92
Fig. 4.3	Group averaged P2 latency results for eye open, eye closed and neutral density filters	94
Fig. 4.4	Group averaged P2 amplitude results for eye open, eye closed and neutral density filters	95

		Page
Fig. 4.5	Group averaged traces of the filter study	96
Fig. 4.6	Group averaged P2 latency results for eye open and eye closed situations with and without a mental task	97
Fig. 4.7	The group averaged traces of the attention study	98
Fig. 4.8	Group averaged P2 latency results for eye open, eye closed, white Ganzfeld and red Ganzfeld	100
Fig. 4.9	Group averaged traces of the Ganzfeld study	101
Fig. 4.10	Group averaged P2 latency results for eye open and eye closed to white light and for eye open to red and green light	102
Fig. 4.11	Group averaged traces of the colour study	103
Fig. 5.1	Circuit diagram of the balanced non-cephalic reference (modified from Stephenson & Gibbs 1951)	110
Fig. 5.2	Traces of EEG showing the elimination of the ECG from the EEG with the balanced non-cephalic reference	111
Fig. 5.3	Traces of a flash VER demonstrating the reproducability of the response	112
Fig. 5.4	Comparison of a stimulus run and a non-stimulus run	114
Fig. 5.5	Brain maps, at 110 msec, of the data presented in Fig 5.4	115

Page

Fig. 5.6	Group averaged traces, to binocular flash stimulation, of all three age groups. Cursored at the latency of the P2 component	119
Fig. 5.7	Brain maps of the group averaged data presented in Fig. 5.6	121
Fig. 5.8	Traces showing the variability in polarity of the component recorded on electrode P3	124
Fig. 5.9	Group averaged traces, to binocular flash stimulation, of all three age groups. Cursored at the latency of the P1 component	127
Fig. 5.10	Brain maps of the group averaged data presented in Fig. 5.9	129
Fig. 5.11	Series of brain maps of the group averaged data of the young age group to binocular flash stimulation at 10 msec intervals	134
Fig. 5.12	Series of brain maps of the group averaged data of the middle age group to binocular flash stimulation at 10 msec intervals	137
Fig. 5.13	Series of brain maps of the group averaged data of the old age group to binocular stimulation at 10 msec intervals	139
Fig. 5.14	Morphology of the waveforms to flash stimulation recorded from a chain of electrodes from the nasion to the inion referred to the chin (after Gastaut & Régis 1965)	142

		Page
Fig. 5.15	Pattern reversal responses recorded to a non-cephalic reference (after Spitz et al 1986)	144
Fig. 5.16	The group averaged traces of all three groups to flash stimulation displayed as if recorded from an Fz reference. Cursored at the latency of the P2 component	150
Fig. 5.17	Brain maps of the group averaged data presented in Fig. 5.16	152
Fig. 5.18	The group averaged traces of all three groups to flash stimulation displayed as if recorded from an Fz reference. Cursored at the latency of P1 component	154
Fig. 5.19	Brain maps of the group averaged data presented in Fig. 5.18	156
Fig. 6.1	Morphology of a typical dark adapted ERG (after Wright et al 1985)	159
Fig. 6.2	The electrode montage used in the ERG study	162
Fig. 6.3	Traces from three young individuals in the ERG study	165
Fig. 6.4	Traces from three old individuals in the ERG study	167
Fig. 6.5	Group averaged traces of the subjects receiving monocular flash stimulation to the right eye	168

		Page
Fig. 6.6	Series of brain maps of the data presented in Fig. 6.5 at 6 msec intervals up to the latency of the P1 component	171
Fig. 6.7	Series of brain maps of the group averaged data to binocular flash stimulation at 6 msec intervals up to the latency of the P1 component	173
Fig. 6.8a	Flash VER recorded from an individual to binocular flash stimulation referred to a BNCR	176
Fig. 6.8b	Flash VER recorded from an individual to binocular flash stimulation referred to a linked ear reference	176
Fig. 6.9a	Flash VER recorded from an individual to binocular flash stimulation referred to a BNCR	177
Fig. 6.9b	Flash VER recorded from an individual to binocular flash stimulation referred to a chin reference.	177
Fig. 6.10	Flash VER recorded from a chain of electrodes running from the inion to CV7 all referred to an ear reference	179
Fig. 6.11	Flash VERs to binocular stimulation recorded from Fz to BNCR, ear to an Fz reference and from the ear to BNCR	181
Fig. 6.12	Group averaged traces of the older age group to pattern reversal stimulation	183
Fig. 6.13	Group averaged traces of the older age group to pattern onset/offset stimulation	185

Page

Fig. 6.14 Brain maps of the group averaged data presented in Figs. 6.12 and 6.13 186

Fig. 6.15 Series of brain maps of the group averaged data to pattern reversal stimulation at 10 msec intervals 191

Fig. 6.16 Series of brain maps of the group averaged data to pattern onset/offset stimulation at 10 msec intervals. 194

LIST OF TABLES

		Page
Table 3.1	The latency values of the components of the flash VER (after Cigánek 1961)	44
Table 4.1	The group averaged data for both the eye open and eye closed state for the older age group	89
Table 4.2	The group averaged data for both the eye open and eye closed state for the younger age group	91
Table 5.1	The group averaged latency and amplitude data for all three age groups, for components recorded at around 100-120 msec, to binocular flash stimulation	123
Table 5.2	The group averaged latency and amplitude data for all three age groups, for components recorded at around 60-75 msec, to binocular flash stimulation	130

CHAPTER 1.

INTRODUCTION

Whether it is feasible for man to ever understand the complexities of the human brain is open to debate. It is likely, however, that its function will remain a subject of intrigue and fascination for philosopher and scientist alike. Man has studied the workings of his own brain from anatomical, physiological, biochemical and psychological viewpoints. The brain, the communications and control centre of the body, comprises of about 1.3 Kg of complex interwoven nervous tissues. Information, relating to the staus quo of the body and its relationship to its enviroment, passes to and from the brain as electrical impulses along the millions of nerves of the peripheral nervous system. The process by which these impulses pass along nerves is well understood, but what occurs when those signals reach the brain and how they are processed remains, for the most part, a mystery.

By means of animal and post-mortem studies of subjects with known functional neurological deficits, areas of the cortex have been ascribed specific functions e.g:- linguistic, motor, auditory and visual function. Animal and post-mortem studies, however, do not necessarily equate with the function of the living human brain. It is important to study the human brain in its normal, in vivo, functioning state. The study of the brain, an organ encased in a strong protective shell, the penetration of which may alter its function and could cause permanent damage, generally make invasive techniques of investigation ethically unacceptable, except in exceptional circumstances. It was Hans Berger (1929) who first recorded the electrical activity of the living human brain through the intact skull. He placed electrodes on the scalp, amplified the signals detected and recorded the first "electroenkephalogram". It was found that

the brain was continually producing electrical activity. With further recordings it became apparent that there were certain patterns of activity common to all human brains e.g:- the frequency range of the electrical activity, and the effect of sleep on the ongoing activity. Thus a method had been found by which the brain could be studied using non-invasive means.

Unlike the random continuous activity of the brain, the electrical response of the brain to stimulation of the visual, auditory or somatosensory system usually occurs at a set time or latency after stimulation, has a definite morphology and is specific to the form of stimulation. The response could only rarely be detected amidst the random background electrical activity of the brain, for example the 'K' complex, until the advent of the averaging computer with which it has become possible to record the potentials evoked by stimulation of all specific sensory pathways. The study of these evoked responses showed that after a period of maturation the response recorded to both auditory and somatosensory stimulation changes very little throughout life. The visually evoked response, recorded as the result of stimulating the visual system by the presentation of a pattern stimulus demonstrates similar post-maturational consistency. However, this is not true of the response to stimulation of the visual system with flashes of light. As the age of the subject increases the number of components of which the response comprises increases. It is interesting that the electrical activity evoked in the brain by stimulation of the visual system by a flashing light behaves differently to stimulation of the visual system with a pattern.

The morphology, latency and amplitude of the electrical signals recorded as a result of stimulation of the visual, auditory and somatosensory systems are reproducible and thus can be used to provide information as to the integrity of those systems. The flash visual evoked potential is used as an aid in the diagnosis of ophthalmological, neurological and psychiatric disorders. The effects of certain disease processes on the latency and/or

morphology of the flash visual evoked response are well documented. The component of the response that is used an indicator or marker of normality is the positive potential recorded at about 100-120 msec after the flash of light. This is known as the P2 component. This is the component which is present throughout the age range, although its latency appears to increase with the age of the subject. The positive potential, at a latency of about 65-75 msec (P1), which appears as the subject ages and is absent in the young, is not generally held to be a reliable diagnostic indicator.

Although the P2 component of the flash visual evoked response is used in diagnostic tests, there is no conclusive evidence as to its exact cortical origin or indeed the route of transmission of the response evoking signal from the eye to the cortex. The topography of the flash visual evoked response at scalp level can be investigated by recording from an array of electrodes placed over the scalp and mapping the electrical response recorded. For many years of visual evoked response studies only one, two or at the most four channels were used. Although using these techniques comparison of one or two sites on each cerebral hemisphere is possible, more detailed locational comparisons could not be carried out. For the studies detailed in this thesis a twenty channel mapping system was used, which, by calculation, generated electrical contour maps of the whole scalp from the electrical activity recorded at an array of electrodes. The aim was to provide information as to the cortical origin of the components of the flash visual evoked response, their generator sites and to propose a route of transmission of the evoking signal from the eye to the cortex. Subjects of varying ages were studied to investigate the changes in response latency and morphology with age. Concurrently it was possible to appraise topographic brain mapping as a means of presenting visually evoked potential data.

CHAPTER 2.

THE ANATOMY AND PHYSIOLOGY OF THE VISUAL SYSTEM.

2.1.0. THE ANATOMY OF THE HUMAN VISUAL SYSTEM

The photoreceptors of the visual system are the rods and cones in the retina of the eye. The rods and cones synapse with the bipolar cells which in turn synapse with the ganglion cells of the retina. The axons of the retinal ganglion cells, which number about one million, pass from the eye, via the optic nerve, to the optic chiasma. At the optic chiasma nerve fibres from the nasal portion of each retina decussate to join the uncrossed temporal fibres of the contralateral eye, thus forming the optic tracts. The optic tract divides on reaching the postero-lateral aspect of the thalamus. The larger portion, which contains 80% of all retinal fibres, passes to the lateral geniculate nucleus (LGN) of the thalamus, whilst the smaller portion, containing small poorly myelinated fibres, passes to the superior colliculus and the pretectal region of the midbrain which lies between the colliculi and anterior to the third ventricle. Fibres which control pupil reactions follow this subcortical pathway. The fibres synapse in the pretectal region and impulses are passed via crossed fibres to the opposite Edinger-Westphal nucleus, although some fibres pass to the ipsilateral Edinger-Westphal nucleus. The efferent pathway is via the third nerve to the ciliary ganglion, then via the ciliary nerve to the sphincter muscle of the iris.

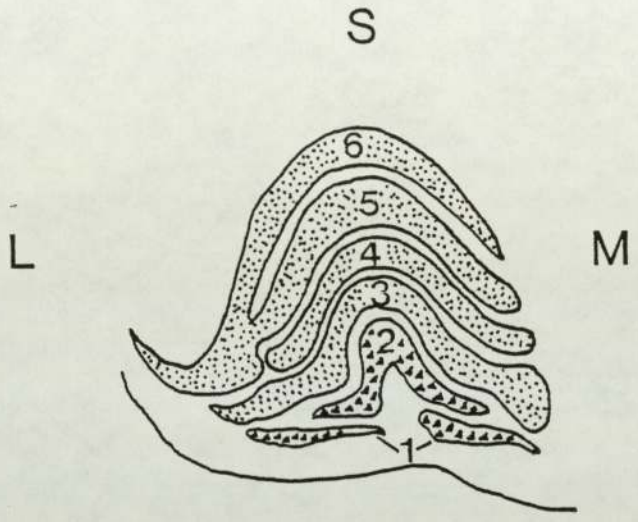


Figure 2.1:- The human LGN in coronal section near its central region showing the two magnocellular layers (1 and 2) and the four parvocellular layers (3-6) after Gray (1973).

A = THE RETINA

B= THE OPTIC NERVE

C= THE OPTIC CHIASMA

D= THE OPTIC TRACT

E= MEYER'S LOOP

F= THE LATERAL GENICULATE NUCLEUS

G= THE SUPERIOR COLLICULUS

H= THE OPTIC RADIATION

I= THE PRIMARY VISUAL CORTEX

Key for Figure 2.2.

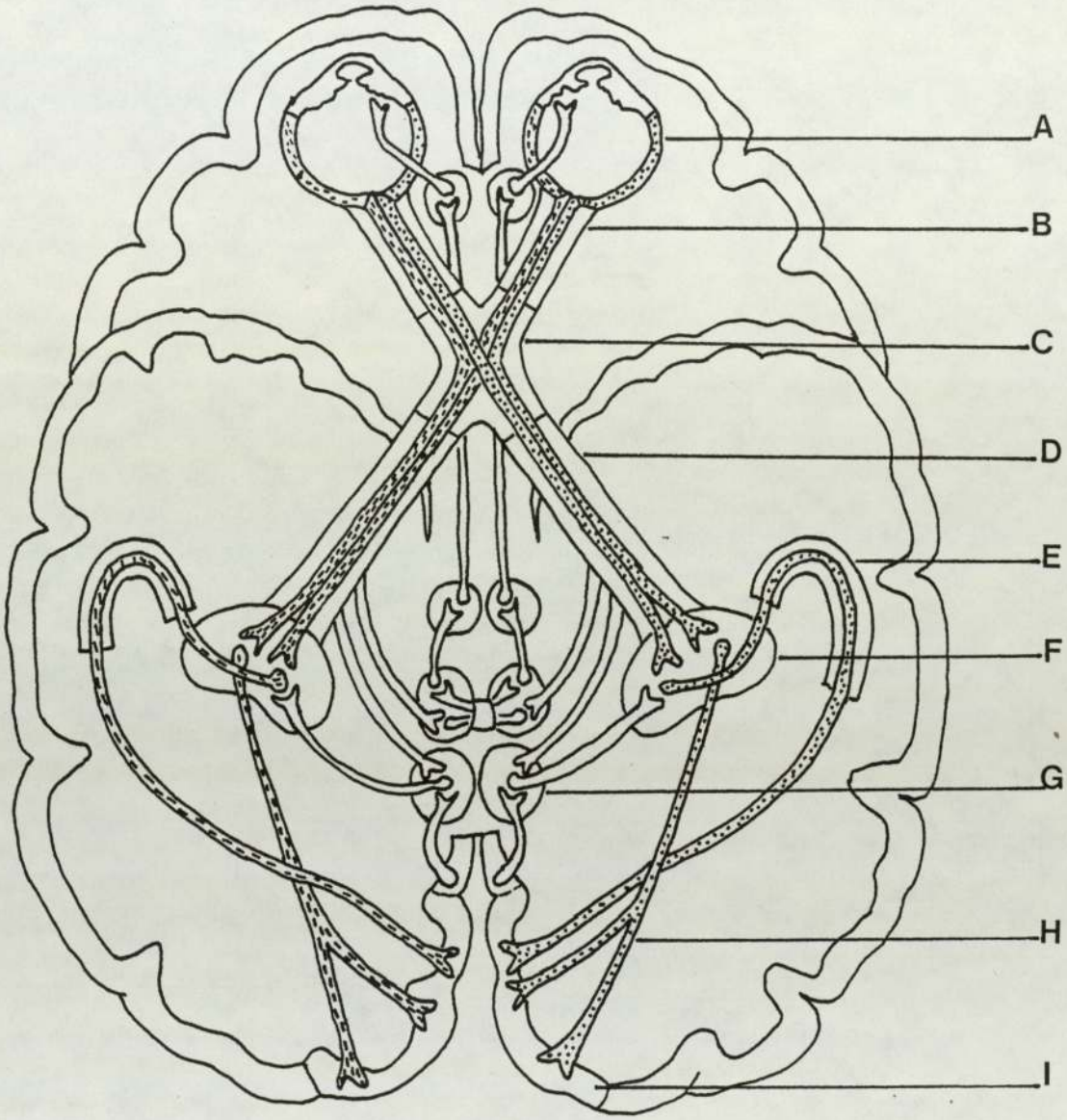


Figure 2.2:- The human visual pathway after Diamond et al (1985).

The LGN lies under the pulvinar and consists of a dorsal and ventral portion. In man the ventral portion is believed to have no visual function. The dorsal portion consists of six layers, numbered 1 to 6 as one moves dorsally. Layers1, 2 and 4 receive crossed fibres from the contralateral eye and layers 3, 5 and 6 receive the uncrossed fibres from the ipsilateral eye (Figure 2.1). From the layered cells of the LGN, the retino-cortical pathway continues via the optic radiation to the visual cortex, in the occipital lobe (Figure 2.2).

The cerebral cortex of man consists of six layers; layer I-the zonal layer, layer II-the outer granular layer, layer III-the pyramidal layer, layer IV-the inner granular layer, layer V-the ganglion layer and finally layer VI-the multiform layer. The striate visual cortex or Brodmann area 17, so called because it possess a distinct darker line on macroscopic inspection (line of Gennari), lines the calcarine fissure, extending above and below the latter as well as forming part of the lateral surface of the hemisphere. The striate cortex differs structurally from other parts of the cortex; layers III, V and VI are thinner than normal, whilst layer I and more especially layer IV are much thicker. In the striate cortex layer IV may be subdivided into three layers; IVa , IVb and IVc. Layer IVc maybe further subdivided into IVcα and IVcβ.

The striate cortex is surrounded by the parastriate cortex, Brodmann area 18, which occupies both medial and lateral surfaces of the occipital lobe and lacks the distinct laminae of layer IV. The peristriate cortex, Brodmann area 19, surrounds area 18, lying mainly on the lateral aspect of the hemisphere and forming the posterior parietal lobe anteriorly whilst inferiorly it forms part of the temporal lobe.

2.2.0. THE PHYSIOLOGY OF THE VISUAL SYSTEM

2.2.1. THE RETINA

In 1953 Kuffler described the configuration of the retinal ganglion cells of the cat. The receptive fields of these cells were found to be concentric, with the discharge pattern of the central region being the opposite of that found in the periphery of the field i.e. if the centre gave an "on" discharge the surround would give an "off" discharge and vice versa. Cat retinal ganglion cells may thus be classified as either "on" centre or "off" centre cells. It has been shown since that monkey ganglion cells show a similar concentric organization (Hubel & Wiesel 1960).

2.2.1a. THE CAT RETINA.

In1966 Enroth-Cugell & Robson first proposed a classification of retinal ganglion cells on the basis of spatial summation. They demonstrated that one group of cells exhibited linear summation in response to a stationary grating stimulus (X-cells), whereas another group of cells responded in a non-linear fashion (Y-cells). Both on-centre and off-centre ganglion cells were common to both groups. Similar findings have been reported by other workers (Ikeda & Wright 1972, Hochstein & Shapley 1976). Enroth-Cugell & Robson (1966) have also shown that in response to a drifting grating pattern Y-cells respond with a mean increase in pulse density of discharge, whilst X-cells respond with a modulation of pulse density at the drift frequency.

Subsequently, further criteria for the classification of the cat retinal ganglion cells were discovered. These included classification on the basis of the type of response an individual cell makes to a stimulus (Cleland et al 1971, Cleland & Levick 1974). All cells will show a rapid increase in discharge rates at the moment of stimulation, but, in some cells the discharge rates will return to the unstimulated level in a matter of seconds despite continued stimulation (Transient cells). Other cells after a small initial reduction, will stay above their pre-stimulus discharge rates for as long as the stimulus is maintained (Sustained cells). X-cells tend to show sustained responses and Y-cells transient responses (Stone & Fukuda 1974). Cleland & Levick (1974) noted a third type of cell which responded sluggishly to a moving target and termed these cells "sluggish cells". These have also been called W-cells (Stone & Fukuda 1974).

Y-cells have been shown to have larger receptive fields (Peichl & Wässle 1979) and to respond to faster moving targets than X-cells (Cleland et al 1971, Cleland & Levick 1974). Y-cells have the fastest axonal conduction velocities, whilst the "sluggish cells" (W-cells) exhibit the slowest. All three groups contain on- and off- centre ganglion cells (Cleland & Levick 1974, Stone & Fukuda 1974). Y-cells may also respond to a sudden movement of a peripheral stimulus outside their receptive field a phenomenon known as the "shift effect" (Cleland et al 1971).

The distribution of the different ganglion cell types approximates to 55% X-like cells, 25% Y-like cells and 12% sluggish cells, with on- and off- centre cells being equally common. The distribution of cell types varies with retinal location, X-like cells being more commonly located centrally and Y-cells peripherally (Cleland & Levick 1974).

Ikeda & Wright (1972) proposed that the linear summation properties of the sustained cells may be related to a functional role of analysis of spatial contrast and form

recognition, whereas the non-linear properties of the transient cells was related to the detection of objects entering visual space which require orientation responses. Some workers preferred to classify retinal cells according to the linearity or non-linearity of their response characteristics rather than the duration of the response. Their objections to the sustained / transient classification were based on the observation that the responses recorded from the cells varied with the adapted state of the eye. When the eye was fully dark adapted all ganglion cells gave a sustained type of response. However, when the eye was light adapted, although within the scotopic range, the responses tended to be transient (Jakiela & Enroth-Cugell 1976).

These classifications of retinal ganglion cells above have been made on the basis of physiology. However, the retinal ganglion cells of the cat may also be divided into three groups anatomically (Boycott & Wässle 1974): alpha cells with large perikarya with a large dendritic tree; beta cells with smaller perikarya and the smallest dendritic trees and gamma cells with the smallest perikarya but dendritic trees of similar size to those of the alpha cells. The alpha and beta cells show an increase in size of both their perikarya and dendritic trees which relates to the degree of displacement from the centre of the retina.

It is possible to relate these anatomical findings to the physiological findings described above. Cleland & Levick (1974) proposed that the brisk transient cells (Y-like) corresponded with the alpha cells, the brisk sustained cells (X-like) with the beta cells and the sluggish (W-like) with the gamma cells on the basis of receptive field size and antidromic conduction times. More detailed work by Cleland et al (1975a) confirmed the earlier proposal that alpha cells corresponded with brisk transient cells (Y-like).

2.2.1b. THE MONKEY RETINA.

The close correlation between structures of the old world monkey and the human visual systems has led to the adoption of the monkey retinal ganglion cells as a model of human retinal ganglion cells, for experimental study. Many different species have been studied and a variety of nomenclature adopted in each case, a fact which has often tended to obscure the value of the work and rendered it difficult to draw valid comparisons between studies. Only the work on macaque and rhesus mokeys, in which cells with similar properties to those of the cat's X- and Y- cells have been identified, will be discussed below.

Gouras (1968) classified the retinal ganglion cells of the rhesus monkey into two groups which he called "tonic" and "phasic". Tonic cells resembled the X-cell of the cat with a sustained response to stimulation by an appropriate wavelength. Phasic cells, like the Y-cells of the cat, gave transient responses and did not exhibit a maintained discharge to a continuous stimulus. Tonic cells received input from one cone mechanism to the centre and from another to the periphery of their receptive fields, whereas phasic cells received inputs from more than one cone mechanism to both the centre and the periphery. Schiller & Malpeli (1977) and de Monasterio & Gouras (1975) used the terms "colour opponent" and "broad band" ganglion cells and were in agreement with Gouras (1968) in that the "colour opponent" cells gave sustained responses, whereas the "broad band" cells gave transient responses to stimulation.

De Monasterio (1978a) looked at the response of the retinal ganglion cells of the macaque to spectral stimulation and to spatial summation. Unfortunately the nomenclature changed again as he referred to type I, type III and type IV cells (similar to those previously descibed in the LGN of macaques (Wiesel & Hubel 1966)). Type I cells

were cone specific, i.e. their centre responses were as the result of stimulation by a single cone mechanism and their periphery responses by a spectrally different one (equivalent to Gouras' tonic cells). Type IV cells received input to their centre and surround from two or three cone types, i.e. a mixed input or a broad band spectral opponency response (equivalent to Gouras' phasic cells). Type III cells had broad band sensitivity, but lacked spectral opponency.

As with previous work on the cat these three cell types were investigated for summation properties. Type I cells showed linear summation and had a more sustained response, whereas types III and IV showed nonlinear spatial summation. The use of a drifting sinusoidal grating showed that the classification of cells into type I, III and IV cells resembled the X- and Y-cell classification in cats (Enroth-Cugell & Robson 1966). A modulated discharge was recorded from type I (X-like) cells, whereas type III and IV (Y-like) cells showed a large mean increase in their discharges.

In 1966 Ogden & Miller had found that the conduction velocity of the optic neurones varied linearly with fibre diameter and that they could be divided into two groups on the basis of velocity of conduction. A further distinguishing feature of types I, III and IV cells were their relative axonal conduction velocities. Types III and IV, phasic or Y-like ganglion cells had faster conduction times than type I, tonic or X-like ganglion cells (Gouras 1969, Schiller & Malpeli 1977, de Monasterio 1978a). As regards location, tonic or type I cells were said to be more numerous and found more commonly near the fovea than phasic or type III & IV cells (Gouras 1968, de Monasterio & Gouras 1975, de Monasterio 1978a). Schiller & Malpeli (1977) did not agree with this finding and proposed an even distribution of cell types throughout the central 20 degrees of the retina.

By no means all retinal ganglion cells of the macaque are centre - surround cells, and hence are able to be classified into types I,III and IV (de Monasterio 1978b). A few fall into another group similar to the W-cells of the cat (Stone & Fukuda 1974). De Monasterio (1978b) subdivided this atypical group into three calling them types II,V and VI. Unlike the cat, where the W-cells were slow conducting cells, in the macaque they fell between the X- and Y- type cells and did not appear to conform to a definite third group.

Studies have been undertaken which attempt to correlate the physiology with the anatomy of the primate retina. Perry & Cowey (1981) using a horseradish peroxidase labelling technique identified two types of retinal ganglion cells which they termed P-alpha and P-beta cells. The P-beta cells, which were most common in the central retina, had small cell bodies, fine axons and the smallest dendritic fields in all retinal locations. P-alpha cells had large cell bodies, thick axons and in all retinal locations the dendritic fields of these cells were larger than those of the P-beta cells. It was concluded that these cells were similar to the alpha and beta cells described in the cat retina. Thus P-alpha cells were the morphological correlate of the monkey's Y-ganglion cells and the P-beta cells the X-ganglion cells based on both field size and conduction velocities. The shift effect in the periphery of the retina demonstrated by the Y-cells of the cat retina (Cleland et al 1971) have also been shown in the monkey (Kruger et al 1975). Shapley & Perry (1986) changed the terminology again, and referred to M and P cells, the equivalent of Perry & Cowey's (1981) P-alpha or Y-like cells and P-beta or X-like cells.

In conclusion the retinal ganglion cells of the monkey can, as in the cat, be classified into W-, X- and Y-like cells with properties common to both species.

2.2.2a. THE CAT LATERAL GENICULATE NUCLEUS.

The X/Y cell classification of the ganglion cells of the cat's retina has been applied to the the cells of the LGN (Cleland et al 1971, Hoffmann et al 1972, Derrington & Fuchs 1979). The cells can be divided into two groups, one group which exhibits linear summation and the other which gives non-linear responses (So & Shapley 1979). The linear summating group give sustained responses and the non-linear group transient responses, correlating well with the previously described X/Y cell classification. Y-cells show the shift effect described for retinal Y-ganglion cells, whilst there is no response from the X-cells (Cleland et al 1971, Derrington & Fuchs 1979).

The X-cells receive slow conducting afferents from the retina and project slow conducting axons to the cortex, whereas the Y-cells receive fast conducting afferents from the retina and project fast conducting axons to the cortex (Hoffmann et al 1972, So & Shapley 1979). W-relay cells have been found to resemble W-retinal ganglion cells (Cleland et al 1975b, Wilson et al 1976, Stanford et al 1981). Wilson et al (1976) showed that each type of retinal ganglion cell relayed to the visual cortex through one lamina in the ipsilateral LGN and two laminae in the contralateral LGN. It appears that the three pathways W-, X- and Y- remain separate but run in parallel from the retina to the visual cortex (Cleland et al 1971, Hoffmann et al 1972, Cleland et al 1975b). Dreher & Sefton (1979) showed that W, X and Y cells can be found in both the laminated parts of the LGN and the medial interlaminar nucleus (MIN) with Y cells being the greatest contributor to the MIN, with W-cells contributing fewer and X-cells the least.

The LGN of the cat consists of five layers, layers, A, A1, C, C1 and C2 (Wilson et al 1976). Morphological studies of the X/Y cell composition of the LGN show that the distribution of X- and Y-cells is different with all the X-cells and most of the Y-cells being located in laminae A and A1. The remainder of the Y-cells are found in lamina C. The X-cell somata are smaller than the Y-cell; X-cell dendrites remained within the lamina in

which the cell was positioned, whereas the Y-cell dendrites crossed laminae. X-cell dendritic trees are asymmetrically elongated whereas Y-cell denditic trees are more radially symmetrical. X-cell dendrites are thin and sinuous, with numerous appendages, whereas Y-cell dendrites are thick, fairly straight and have few appendages. Finally, although both had collaterals within the LGN these are more commonly seen in Y-cells than X-cells. In both X- and Y- cells the size of the soma correlates with the size of the dendritic tree. It is thought that one third of the neurones are Y-cell relays and the other two thirds are X-cell relays (Friedlander et al 1981). W-cells had small to medium somata and fine dendrites, orientated roughly parallel to the plane of the geniculate laminae borders. The W-cells may be subdivided by the nature of their dendrites (Stanford et al 1981).

Mitzdorf and Singer (1977) used current source density analysis to investigate the laminar segregation of the retinal afferents in the cat LGN. They confirmed that X- and Y-afferents terminated in different parts of laminae A and A1. The X-like synapses were found centrally or to the dorsal side, whereas the Y-like synapses were nearer the ventral border. X-like activity was stronger in lamina A than A1 and Y-like activity showed a reverse pattern.

2.2.2b. THE MONKEY LATERAL GENICULATE NUCLEUS.

Anatomical studies of the LGN of the monkey show that small cells maybe found in the four dorsal or parvocellular layers and that large cells maybe found in the two ventral or magnocellular layers (Wiesel & Hubel 1966). The cells of the monkey LGN maybe classified into X/Y like cells: it has been shown that the parvocellular layer receives input from the X-cells of the retina and the magnocellular layer from the Y-cells of the retina

(Dreher et al 1976, Schiller & Malpeli 1978, Leventhal et al 1981, Perry et al 1984). Many workers agree that the cells in the LGN may be divided into two functional groups on the basis of spatial summation that the X-type cells are confined to the parvocellular layers, however, is subject to debate. Studies have shown that around 95% of the cells in the four parvocellular layers, and 80% in the two magnocellular layers, are X-cells, with the remainder being Y-cells (Blakemore & Vital-Durand 1981, Shapley et al 1981, Kaplan & Shapley 1982). Most agree that the magnocellular layers showed higher contrast sensitivity and have a shorter latency of response to electrical stimulation of the optic chiasma. It maybe concluded that the LGN of the macaque contains parvocellular X-cells, magnocellular X-cells and magnocellular Y-cells, the magnocellular layers being the pathway for contrast vision near threshold, whilst the parvocellular layers maybe involved with the cortical analysis of coloured patterns and pattern contrast. Shapley and Perry (1986) agreed that two types of cells with different visual and spatial filtering properties were found in the magnocellular layer (magnocellular X-cells and magnocellular Y-cells). They also proposed that there is no functional equivalent in the cat for the monkey P-cell (X-like). They concluded that the cat X-cells subserved fine detail and pattern detection and Y-cells signal change and movement whilst in the monkey M-cells (Y-like) were involved in pattern vision and fine detail, and P-cells in colour vision and fine detail at high contrast. Stone (1983) agreed there was confusion, but thought that the parvocellular layers were X-cells and magnocellular layers were Y-cells. Derrington and Lennie (1984) also found only a single type of cell in the magnocellular layers of the macaque, the responses of which, however, were not non-linear.

The cells from the parvo- and magnocellular layers subsequently project to area 17 of the visual cortex.

2.2.3. THE OPTIC RADIATION.

Y-cells in the optic tract of the cat have faster conduction velocities than X-cells (Cleland et al 1971, Hoffmann et al 1972, Bullier & Henry 1979) and in turn the conduction velocities in the optic radiation are faster than for the optic tract especially amongst the X-cells. Optic tract velocities of the monkey are less than those in the cat (Mitzdorf & Singer 1979).

2.2.4. THE VISUAL CORTEX.

As previously stated, the receptive fields of the LGN are like those of the retinal ganglion cells, having a concentric, centre-surround pattern of organization, whereas in the visual cortex the cells are more complex than this and maybe divided into "simple" and "complex" cells (Hubel & Wiesel 1968, Hubel 1982). Simple cells are like retinal or LGN receptive fields in that they have antagonistic surround regions which, when illuminated, increase or decrease the firing of the cell. These antagonistic regions are not concentrically organised. The antagonistic regions of the simple cells are separated by parallel lines the orientation of which produces one of the cells' most important properties, e.g. stimulation by diffuse light or light at 90° to the orientation of the cells' antagonistic regions produces no electrical response.

Simple cells in the cat are found mainly in layer IV of the cortex the layer in which most of the afferents of the LGN terminate. In the monkey the afferents from the LGN terminate in layer IVc, where the cells appear to be of the concentric centre-surround type. The simple cells lie immediately superficial to layer IVc. Complex cells are not so

orientation-specific and will respond if the stimulus falls anywhere within their receptive fields. However, if the stimulus is of the correct orientation then the response will be much more powerful providing the stimulus is kept moving. Some complex cells respond much better to a stimulus with a particular direction of movement, than to any another. These maybe termed "directionally selective".

Hubel & Wiesel (1968) described a feature of complex cells which they called "end-stopping". This is seen when a cell is more responsive to the end of a line rather than a point within a line stimulus, such cells were originally termed "hypercomplex" cells but were later termed "end-stopping" simple cells.

The complex cells may be ascribed to various subtypes, distributed throughout the layers of the visual cortex. In layers II and III the cells have orientation specificity, small receptive fields, low spontaneous activity, are wavelength specific and may or may not be "end-stopped". In layer V the cells are highly spontaneous, responding both to short and long moving lines, and in layer VI the cells respond best to long lines. The cells in the upper layers project to other cortical areas. Cells in layer V project to the superior colliculus, pons and pulvinar, and cells of layer VI project back to the LGN (Gilbert 1977, Gilbert & Wiesel 1979).

Besides the division into different cell types the visual cortex is organised into orientation columns i.e. columns which contain cells with a common receptive field orientation, and ocular dominance columns i.e. columns which contain cells which all relate to the same eye.

2.2.4a. THE CAT VISUAL CORTEX.

It is thought that the X-cells lying mainly in laminae A and A1 of the LGN, with a smaller number from lamina C, project to area 17 of the cat's visual cortex, where they terminate in layers IVc and VI and possibly in the lower part of layer III. Y-cells project to areas 17, 18 and 19. The projections to area 17 terminate in layer IVab, layer III - IV border and layer VI, and arise mainly in laminae A and A1 although a smaller number arise from lamina C and the MIN. The projections to area 18 probably derive from lamina C and the MIN (LeVay &Ferster 1977, Hollander & Vanegas 1977, Leventhal 1979). The W cells from lamina C and the MIN project to layer I, deep regions of layer III and the IV-V border in area 17 (Leventhal 1979).

Layer IV, whose cells are virtually all simple cells, is the first level of cortical processing. Layers II and III represent the second level of cortical processing and are comprised almost exclusively of complex cells. They are pyramidal cells and their axons extend to layers I and V. Layer V cells are also complex cells like those in layers II and III but have larger field sizes. The complex cells of layer V maybe subdivided into two groups; one whose axons project principally to layer VI and to a lesser extent to layer I, and the other whose axons project to the superior colliculus. Layer VI has both simple and complex cells and therefore is comprised of both stellate and pyramidal cells. Their axons project mainly to layer IVab (Gilbert 1977, Gilbert & Wiesel 1979). The majority of simple cells are stellate whereas most complex cells are pyramidal (Kelly & Van Essen 1974).

Dreher et al (1980) investigated the afferent input to the cat's visual cortex by examining receptive field properties and the cellular response to electrical stimulation. They found that the majority of cells in area 19 were driven by W type afferents although a few were driven by direct acting Y-afferents. It appeared that the majority of Y-afferent input to area 19 arrived indirectly via another region of the visual cortex. The vast majority of cells

in area 18 appeared to be driven by Y-like afferent input, whereas area 17 received input from all three types of afferent cells (W-, X- and Y-like). Other workers have also proposed that the input to cells in the cat's visual cortex can be described as X- or Y- in type (Gilbert & Kelly 1975, Martin & Whitteridge 1981).

Gilbert and Kelly (1975) found projections from the pulvinar to areas 17,18 &19 and from the MIN to areas 17 &18. Movshon et al (1978) found that the neurons in area 17 responded to low frequency stimuli and less well to high frequencies whilst the neurons in area 18 responded to a stimulus range of 2 - 8 Hz. They postulated therefore that area 17 was involved with pattern recognition and area 18 with movement recognition.

As previously described the cells of the visual cortex of the cat may be divided into simple and complex types (Hubel & Wiesel 1968). There is some controversy as to whether simple and complex cells receive information from different sources and whether visual information is processed in parallel or in series. Some workers claim simple cells correspond to the X-system and complex cells to the Y-system, whilst others state that there is no clear relationship between afferent input and receptive field type. Singer et al (1975) used an electrical stimulation technique to divide the cortical cells of the cat into two groups; group I resembled simple cells and group II resembled complex cells. They found that group I cells were driven mainly by LGN afferents and group II cells were driven from converging inputs from LGN afferents with occasional additional input from callosum and recurrent collaterals of corticofugal axons. However, they found that cells in both groups could be driven by both X- or Y- afferents. Ikeda and Wright (1975a) defined two classes of feline cortical cells with similar properties to those of retinal ganglion cells i.e. sustained or transient responses. Simple cells could show sustained or transient response characteristics, as could complex cells. This contradicted the work of Hoffmann & Stone (1971) who, on the basis of conduction

velocity studies, hypothesised that complex cells were driven by Y-like afferents, whilst the simple and hypercomplex cells were driven by X-like afferents. In a further paper Ikeda & Wright (1975b) looked at the distribution of cortical sustained and complex response cells. The sustained response cells were found in areas of the cortex primarily concerned with receiving projections from the central retina, whereas transient response cells were found in areas concerned with peripheral vision. They did not find a similar division in the distributions of simple and complex cells, suggesting that a direct relationship between X-afferents and simple cells, and Y-afferents and transient cells does not exist.

2.2.4b THE MONKEY STRIATE CORTEX.

The majority of the cells of the monkey LGN project to area 17 of the visual cortex, there is controversy as to whether there is a direct projection to the prestriate cortex (Yoshida & Benevento 1981, Yukie & Iwai 1981, Hendrickson et al 1978). By means of single cell recordings Hubel and Wiesel (1972) showed that lesions in the parvocellular layers of the LGN of the monkey led to degeneration in layer IVc (now called IVcβ) together with a small portion of the upper part of layer IVa, as well as some degeneration in layer I. Lesions in the magnocellular layers led to degeneration in layer IVb (now called IVcα), and in IVc (IVcβ) but not in layers IVa or I. They also discovered that the ocular dominance columns shown physiologically could be demonstrated anatomically. Various workers since have looked at the terminations of the LGN afferents in the monkey. They agree that the afferents from the parvocellular layers terminate in layer IVcβ and those from the magnocellular layers terminate in layer IVcα (Lund et al 1979, Blasdel & Lund 1983, Blasdel & Fitzpatrick 1984). Blasdel & Lund (1983) showed that the afferents from the LGN terminated in five different layers. These were the upper and

lower parts of layer IVcα, layer IVcβ, layer IVa and layer I. The input to all these layers except for layer IVcα was apparently from the parvocellular layers. There is believed to be no thalamic input to layer IVb of the monkey (Lund et al 1979, Blasdel & Fitzpatrick 1984).

Mitzdorf & Singer(1979) applied the theory of 'current source density' to intracortically recorded field potentials resulting from electrical stimulation of the primary afferents in the macaque. They found that in area 17 the cells could be divided into two groups on the basis of their fast or slow conducting afferents. The fast afferents derived from the magnocellular layers, had monosynaptic activity in layer IVcα and layer VI, disynaptic activity in layer IVcα and in the supragranular layers, and trisynaptic activity in layer IVb. The slow afferents derived from the parvocellular layers had monosynaptic activity in the lower part of layer of IVcβ and layer VI, disynaptic activity, via strong connections, in the upper parts of layer IVcβ, layers III and IVb, and trisynaptic activity in layers Va and II. They found no slow afferent activity in layer I, although in area 18 both slow and fast afferents were found in layer IV and it was thought likely that they were mediated by the monosynaptically activated cells in area 17. Activity latencies in the monkey were found to be much slower than those of the cat probably because the fibres involved were much thinner. However, in both species the fast conducting afferents finished above the slow conducting afferents in area 17.

Lund (1973) identified four cell types within the visual cortex of the monkey; pyramidal cells, stellate cells with spiney dendrites and stellate cells which were spine free or sparsely spined. The spiney stellate cells were found only in layer IV, spine free stellate cells in all cortical layers, sparsely spined cells in all layers except layer IV and pyramidal cells in all layers except layer IVc.

Lund & Boothe (1975) found that the stellate cells in layers IVa and IVcβ received input from the parvocellular layers of the LGN, sent axons to layers III and V (where they synapsed with the apical dendrites of those pyramidal cells with somas in layer VI) and projected back to the parvocellular layers of the LGN. Stellate cells in layer IVcα were found to receive input from magnocellular layers, to spread within that layer and layer VIb and also to synapse with the apical dendrites of pyramidal cells of layer VI (which in turn project back to the magnocellular layers of the LGN.)

2.2.5. THE MONKEY PARASTRIATE AND PERISTRIATE CORTEX.

The Brodmann equivalent of the parastriate cortex is area 18 whilst for the peristriate cortex it is area 19. Another method of classification is to refer to the visual area which is not striate cortex as prestriate cortex and this would include both areas 18 and 19. This prestriate cortex may be divided in to four visual areas V2, V3, V3a and V4. V1 being the striate cortex (Cragg & Ainsworth 1969, Zeki 1971).

Over 70% of cells in V2, V3 and V3a are orientation selective but only 8% are selective for colour, the latter lie in V2. Around 54% of cells in V4 are colour selective but less than 50% are orientation selective (Van Essen & Zeki 1978, Zeki 1978a). Zeki (1978b) looked at the projections the prestriate received from the striate cortex. Areas V2 and V3 received both foveal and extrafoveal striate projections directly, whereas V4 received foveal striate projections direct whilst any extrafoveal projections were relayed via V2. Yukie & Iwai (1981) looked at the LGN projections to the prestriate cortex of the monkey by the use of retrograde degeneration techniques. Retrograde degeneration of the LGN was produced by injection of the striate cortex and prestriate cortex with

horseradish peroxidase, it did not occur with injection of the inferotemporal and parietal regions. The LGN degeneration was greatest with injection of the striate cortex. Injection of the prestriate cortex highlighted cells in the LGN with ovoid, fusiform or triangular forms, whereas the cells identified by injection of the striate cortex were uniformly ovoid or round. They postulated from this that there were two pathways to the prestriate cortex of the monkey from the LGN, a direct one and an indirect one via the striate cortex. A direct pathway was supported by the work of Yoshida & Benevento (1981) who identified a direct projection from the LGN to layers IV and V of the prestriate, predominantly to area 19 and the anterior part of area 18. It was unclear as to whether these LGN cells received retinal input. This contradicted the work of Hendrickson et al (1978) who stated that there was no direct LGN - prestriate pathway.

2.2.6. EXTRAGENICULATE PATHWAYS.

2.2.6a. THE EXTRAGENICULATE PATHWAYS IN THE CAT.

It is thought that only the W- and Y- cells of the cat project to the superior colliculus (SC). The Y-cell afferents branch so that the SC and LGN receive afferents from the same ganglion cells, whereas the W-cell afferents do not branch substantially and project either to the SC or to the LGN. The SC receives input from all cortical regions (Stone 1983).

2.2.6b. THE EXTRAGENICULATE PATHWAYS OF THE MONKEY.

The evidence as to the nature of an extrageniculate pathway from the retina to the visual cortex of the monkey and its function is unclear. In the monkey, cells projecting to the SC lack colour opponency and a high percentage of the cells are rarely encountered cells or W-like cells (Schiller & Malpeli 1977, de Monasterio 1978b). Besides showing a lack of colour opponency they have slow conduction velocities and exhibit non-linear summation. Marrocco & Li (1977) concurred with the observation that the cells of the SC were chromatically non-opponent and wavelength tuning was non-existent.

The number of retinal axons which branch to reach the SC from those going to the LGN is limited, Perry & Cowey (1984) thought less than 10%. Y-like and to a greater extent W-like cells, are the vast majority of cell types which project to the SC and their afferents terminate in different layers of the SC (Stone 1983). Perry & Cowey (1984) found the cell types present in the SC were mainly P gamma cells and P epsilon cells, occasionally P alpha cells, but never P beta cells. They also thought that the cells which projected to the SC were completely different from those cells which projected to the LGN.

The SC has no direct projection to the visual cortex (Goldberg & Robinson 1978) but projects to the pulvinar which in turn projects to areas 17 and 18, the projection to area 18 being the larger.

2.2.7. SUMMARY.

The evidence for a parallel processing system from the retina via the dorsal LGN to the striate cortex, area 17, both in the cat and the monkey is well proven and maybe used as

a model of the human visual system. On reaching area 17 it is open to debate as to whether there is parallel or serial processing or a combination of the two. The functional role of the separate W-, X- and Y- like cells is thought to differ between the cat and the monkey. The parvocellular cells of the monkey are thought to be concerned with colour vision and fine detail at high contrast, whereas the cells of the magnocellular layers are thought to be concerned with pattern vision near threshold. In the cat the X-cells are thought to subserve fine detail and pattern detection and Y-cells signal change and movement.

The role of the extrageniculate pathways in monkey and human vision is unclear. The superior colliculus in the human visual system is believed to be a reflex centre mediating complex somatic reflexes e.g. starting and tensing at a flash.

CHAPTER 3.

THE FLASH VISUAL EVOKED RESPONSE.

3.1.0. THE COMPONENTS OF THE FLASH VISUAL EVOKED RESPONSE.

An evoked potential is a fluctuation in the background electrical activity of the brain elicited by a specific stimulus. The introduction of averaging techniques, (Dawson1954), and the use of gated time locked sampling have made evoked potential recording possible. After the presentation of the stimulus an epoch of incoming signal is amplified, recorded and stored. It is then added to the subsequent incoming epoch of signal after the next stimulus presentation. This procedure is repeated a number of times and the resultant record is then divided by the total number of epochs used in the averaging period to produce a final trace which reflects the time locked activity of the evoked potential. The background brain activity has a random relationship to the stimulus and will tend to cancel itself out during the averaging (Figure 3.1). Thus a small evoked potential, which would otherwise be lost in the background activity, becomes detectable.

Research into visual, auditory and somatosensory evoked potentials has expanded, aided considerably by the advent of computers able to provide rapid online averaging. This has enabled evoked potential recording to become part of clinical practice.

A visual evoked response (VER) can be recorded to a luminance stimulus, e.g. a flash of light, - (The 'Flash' or 'Photic' VER) or to a patterned stimulus e.g. a reversing checkerboard pattern, - (The Pattern Reversal VER). The waveform of the response recorded is dependant upon the stimulus used.

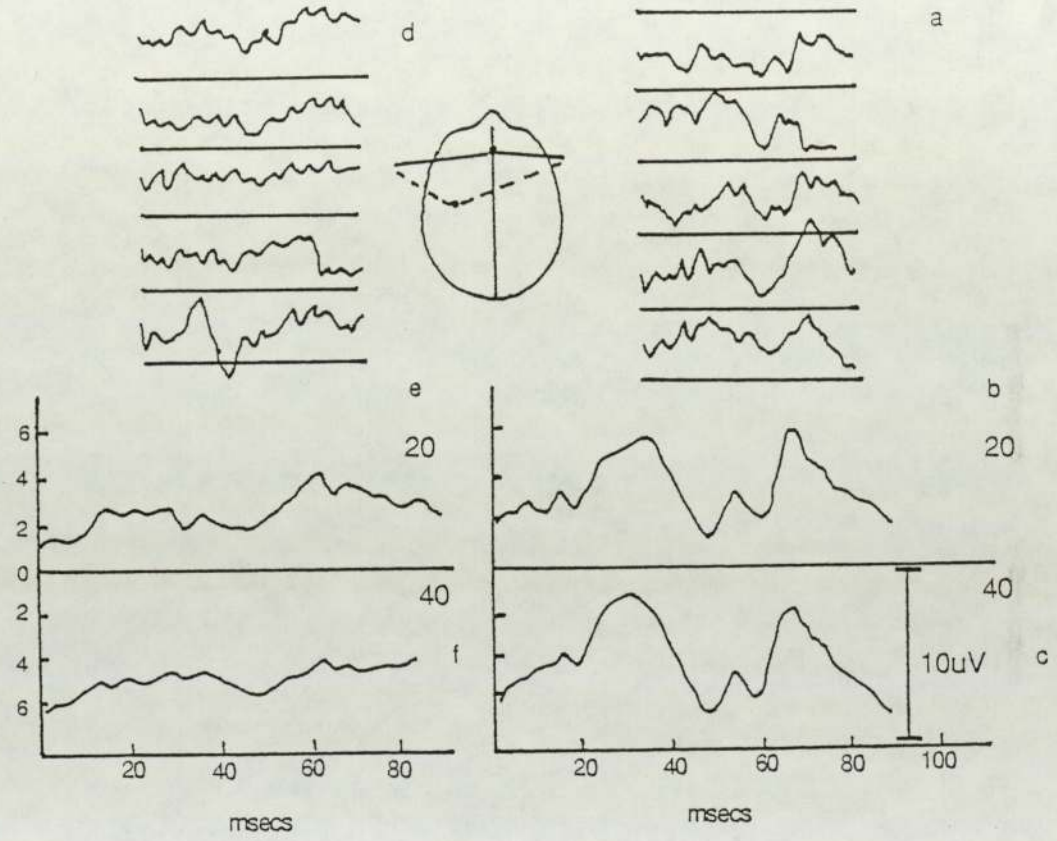


Figure 3.1:- after Dawson (1954) showing the principles of averaging. The right handside of the figure shows the raw EEG when a stimulus was applied to the right arm and recorded from the left scalp. In the top traces (a) the responses are not clear amongst the spontaneous activity. The averages of 20 and 40 records are shown in (b) and (c). On the lefthandside of the figure in (d) shows raw EEG when no stimulus was applied. The averages of 20 and 40 records are shown in (e) and (f).

Patterned stimuli were developed to excite the pattern detectors of the visual system, and not the luminance channels. It is essential that the average luminance of the target is kept constant throughout the stimulus cycle to prevent the production of an additional luminance response. Two types of pattern stimuli are used routinely in the clinical situation - pattern reversal and pattern onset / offset (Wright 1985).

Cobb & Dawson (1960) described four major components of the flash VER: an occipital positive potential at a latency of around 20-25msec, a negative potential peaking at around 40-50 msec, a larger positive potential peaking at about 55-65 msec and a large negative potential peaking at around 90-100 msec. A number of waves at around 100 msec were recorded after the 4th major component. They found their results were reproducible not only over a period of minutes, but over a matter of months.

Cigánek (1961) summarized his experience of recording flash VERs over a period of three years. He identified seven reproducible components which he labelled I to VII. The response was localised mainly over the centre line of the occipital region of the visual cortex (Figure 3.2). The latencies of the components identified are given in Table 3.1 below:-

Table 3.1:- The latency values of the first six components of the flash VER described by Cigánek (1961).

COMPONENT	LATENCY(msec)	STANDARD DEVIATION
Wave I	28.62	4.76
Wave II	53.40	4.42
Wave III	73.33	6.36
Wave IV	94.19	7.13
Wave V	114.00	7.41
Wave VI	134.55	9.92

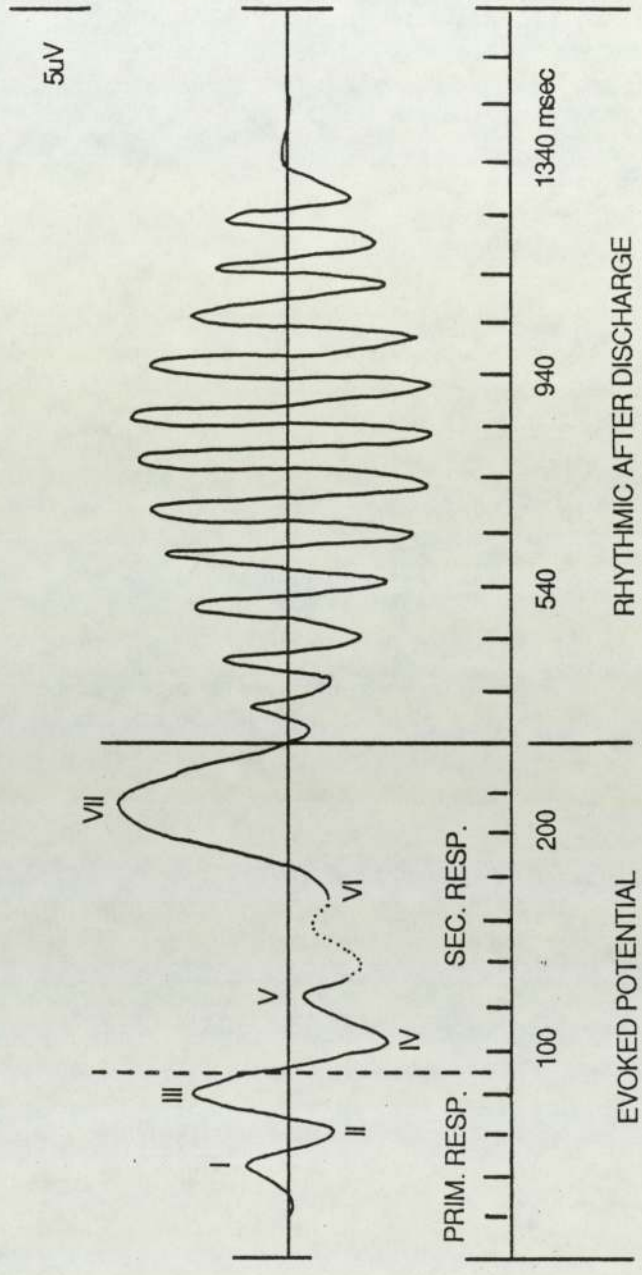


Figure 3.2:- The waveform of the flash visual evoked response described by Cigánek (1961) with the seven identified components labelled.

Waves I to III he termed 'the primary response', postulating that this part of the response was evoked in Brodmann area 17 of the visual cortex, the stimulus having followed a specific rapidly conducting pathway to the cortex, whereas the secondary response, waves IV to VII, was thought to be the result of conduction via ill defined, non-specific, slower conducting pathways.

The morphology of the response described above has been supported by several other authors (Kooi & Bagchi 1964, Heath & Galbraith 1966, Gastaut & Régis 1967, Dustman & Beck 1969, Harding 1974). The nomenclature used for the naming of the individual components varies amongst authors. A stylised flash VER is shown in Figure 3.3, the components of which are labelled by the various systems.

3.2.0 PROCEDURES FOR RECORDING THE FLASH VISUAL EVOKED RESPONSE.

3.2.1 ELECTRODES.

Electrodes are required to convert ion flow in the living tissue into an electron flow in an electronic circuit. There are two categories of electrodes; scalp electrodes, which are placed on the surface of the scalp, and intracortical electrodes, which are inserted inside the skull. The use of intracortical electrodes is rarely permissible in normal healthy volunteers. Heath and Galbraith (1966) compared the response to flash stimulation recorded from both intracortical and scalp electrodes in two human patients and found the responses were very similar for components up to100 msec. Van der Marel et al (1984) also found a good correlation between scalp and skull recorded VERs in the rhesus monkey. Corletto et al (1967) in per-operative studies on a patient with occipital epilepsy found that the response recorded to flash stimulation from electrodes placed

	A	B	C	D	E	F	G	after Dustman & Beck (1969)
	I	II	III	IV	V	VI	VII	after Cigánek (1961)
1	2	3	4	5	6			after Gastaut & Régis (1967)
P0	N1	P1	N2	P2	N3	P3	N4	after Harding (1974)

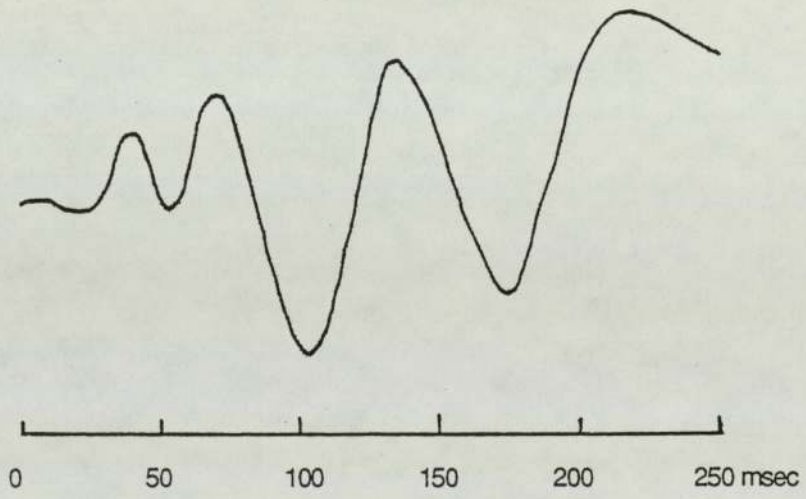


Figure 3.3:- A styalised flash visual evoked response showing the different labelling systems employed by various authors for the individual components of the response. after Harding (1974).

on the surface of the brain in the visual region was very similar to the response recorded from the equivalently placed scalp electrodes. The disadvantage of scalp electrodes is that they record activity from a widespread area of cortex and not just from the specific area of cortex over which the electrodes are placed. Caution is therefore required in the interpretation of scalp recorded responses with regard to the anatomic origin of the recorded response. The non-invasive scalp electrode is however, the best compromise available at present for recording evoked potentials from human subjects or patients, and was used throughout the studies described here.

There are many types of surface scalp electrodes; cup or disc electrodes, suction electrodes and pad electrodes. The most commonly used electrodes are the cup or disc electrodes, which are about 10 mm in diameter, made of chlorided silver to which a lead is soldered. The electrode is attached to the scalp either by gluing or by strips of adhesive tape. To improve the contact between the scalp and the electrode, electrode jelly is inserted under the electrode using a syringe, via a hole in the top of the electrode. Skin electrode resistance should be reduced below 5 kΩ. This can be achieved by either gently abrading the scalp with a blunt needle or by the use of Omniprep an abrasive paste (D.O. Weaver & Co. 565-C Nucla Way, Aurora, CO. 80011 USA).

Suction electrodes are sometimes used in neonates. They are filled with electrode jelly and, as their name implies, suction is achieved by squeezing and releasing an attached suction bulb, whilst the electrode is held against the skin.

Pad electrodes consist of a silver chloride stud which is padded with sponge and gauze, and supported by a plastic foot. Each is soaked in saline prior to use and is attached to the head by means of a harness.

To standardise the location of scalp electrodes an international system has been devised, 'The 10-20 system' (Jasper 1958). The system is based on constant anatomical landmarks, with each electrode being placed a set proportion of the distance along lines connecting these landmarks e.g. inion to nasion. Each electrode position is given a letter to identify the area of brain over which it is located and a number indicating the side of the underlying hemisphere. Even numbers are located over the right hemisphere and odd numbers over the left hemisphere. The system was originally designed for electroencephalographic (EEG) studies, but can be adapted for evoked potential work. Extra electrodes can be sited between existing electrodes and the numbering system modified.

Homan et al (1987) used a computer assisted tomographic (CT) scan to assess how closely the scalp electrodes matched their supposed cortical position. The 10-20 system provided scalp locations which correlated well with the expected cerebral structures for the majority of subjects.

3.2.2. THE REFERENCE ELECTRODE.

All electrophysiological records measure the potential difference between an active electrode or electrodes and some form of reference electrode. The morphology of the waveform recorded at a given electrode site is dependant upon the reference site chosen (Lehmann & Skrandies 1980). The chosen reference will not alter the absolute potential difference between two points within the field, but enables all the potentials within the field to be measured relative to the potential which exists at the reference electrode.

References can be of various types; common, bipolar, average and balanced non-cephalic. Common referencing assumes that the reference electrode is inactive

relative to the evoked activity on the active electrodes, although ideally equipotential to the active electrodes with respect to myogenic activity, artefact or interference potentials (Goff 1974). All active recording electrodes are referred to this single reference electrode. A number of reference electrode positions have been used by different workers as the common reference site for the flash VER e.g. linked ears (Kooi & Bagchi 1964, Borda 1977), the midfrontal electrode (Halliday et al 1972, Mushin et al 1984, Wright et al 1985), the central electrodes (Harding 1977, Harding & Crews 1982), ipsilateral mastoid (Skalka & Holman 1986) and chin (Gastaut & Régis 1965).

Bipolar recording is mainly used in routine EEG work where the first electrode in a chain of electrodes is referred to the second electrode and the second electrode is referred to the third electrode and so on. This method is useful as a phase reversal of components in the chain of electrodes will indicate the position of a locus of activity. Phase reversal results from an electrode being the grid II electrode in one pairing and the grid I electrode in the other. If a positive potential is present under that electrode, it will show as an upward deflection on the first trace and as a downward deflection on the second trace. Bipolar recording is not commonly used for evoked potential work as unless the electrode spacing is sufficiently large any localised activity will be picked up on all electrodes and the phase reversal of components will not be evident. Although not commonly employed, bipolar referencing is used in evoked potential work in some clinical situations. Harding et al (1969) described a bipolar montage for the recording of visual evoked potentials originally to aid in the diagnosis of visual field defects. Evoked potentials are recorded from six channels:- channel 1 O2-C4, channel 2 O1-C3, channel 3 T5-O2, channel 4 O2-T4, channel 5 T6-O1 and channel 6 O1-T3. There will be phase reversal on channel 3 and 4 if there is a signal arising from under electrode O2 and the same will apply to channels 5 and 6 if the signal originates under electrode O1. Using this system Harding et al (1969) were able to locate precisely from which hemisphere a response was originating.

Offner, in 1950 described average reference recording for EEG work. He connected all his electrodes together through, high resistances, and then used the common junction as the reference. Thus, if a large potential was recorded on a single electrode it would be recorded on the other channels with reversed polarity and a reduced amplitude, the latter being a function of the number of electrodes used in the average. Offner in suggesting average referencing for EEG recording assumed that the signal was generated by a large number of current dipoles of random orientation, so a constant mean value near zero could be achieved. Evoked potentials, however, are not random signals and Bertrand et al (1985) warned of the limitations of average reference recording in evoked potential work. Electrodes should be placed over both hemispheres and ideally all over the head not just on the top half as in the 10-20 system. The use of average referencing for evoked potential work however, is advocated by some workers (Lehmann & Skrandies 1984).

The problem with all common reference sites placed on the scalp is ensuring inactivity of the reference electrode. To try and overcome this problem Stephenson & Gibbs (1951) designed the balanced non-cephalic reference (BNCR). One electrode is placed on the right sterno-clavicular joint and the other is placed on the spinous process of the seventh cervical vertebra, the vertebra prominens. The two leads are joined via two variable 20 kΩ potentiometers which are adjusted to balance out the electrocardiogram (ECG). It has been shown to be inactive for both visual and auditory evoked potential recording but active for somatosensory evoked potential recording (Lehtonen & Koivikko 1971). Several workers have used non-cephalic or the balanced non-cephalic reference for both evoked potential recording and for routine EEG work (Spitz et al 1986, Ropper et al 1978, Rugg et al 1985, Shih et al 1988). The complete elimination of the ECG at times can be a problem and may result in additional time being added to the recording session.

3.2.3. AMPLIFICATION.

The electrodes are plugged into a differential amplifier, which is designed to amplify the difference in potential between two inputs. Thus a differential amplifier will only amplify antiphase potentials and is insensitive to inphase potentials; this property is called the common mode rejection ratio. The value of this is in the elimination of non-neural input to the system such as eye movement, muscle artefact or mains interference.

The amplifier also increases the size of the signal (signal gain). Amplification is defined as the voltage output of an amplifier divided by the voltage applied to the input.

The input filters used in the recording of visual evoked potentials can have an important effect upon the response recorded. Filters can be used to filter out high frequencies and / or low frequencies. A high frequency or low pass filter will remove frequencies above a set frequency, whereas a low frequency or high pass filter will remove frequencies below a specified number of Hertz. Jutai et al (1984) performed a spectral analysis of the flash visual evoked potential. They recorded responses from electrodes over the occipital, temporal, and central regions of the scalp. The dominant frequencies of the response recorded from the vertex and temporal regions were 2-6 Hz whereas the dominant frequencies of the response from the occipital region had a wider range of 2-14 Hz. Therefore, when recording a flash VER the setting of the high and low pass filters at 0.3 and 30 Hz respectively is appropriate as the frequency of the response to be recorded falls within the range.

Additionally there are notch filters which remove input of a specific frequency band e.g. 50 Hz or mains interference.

The ability to smooth a recorded waveform is another facility provided by modern day averagers. The waveform displayed, on the completion of the predetermined number of

presentations, is a line drawn exactly through each data point in turn. When a waveform is smoothed the average of three successive data points is taken and the trace is drawn through the averaged points. Three point smoothing is the most commonly applied method although a greater number of data points theoretically could be averaged. Caution should be taken in smoothing waveforms as in reality smoothing has a secondary filtering effect. One situation where it may be acceptable to smooth a waveform is to reduce low amplitude noise on a high amplitude waveform.

3.2.4. STIMULATION.

As previously stated visual evoked potentials can be recorded to a luminance stimulus e.g. a flash of light, or to a patterned stimulus e.g. a reversing checkerboard pattern. The waveform of the response recorded is dependant on the stimulus used.

The ideal way to control luminance stimulation is by means of a Maxwellian view system (Goff 1974). Maxwellian view presents the light focused to a point on the cornea. The light then expands, beyond the focal point, to stimulate a section of the retina whose area is not dependant on pupil diameter. The main disadvantage of this system is that the head has to be held rigid by means of a bite bar which should be individually made for each subject or patient. The bite bar produces problems for evoked potential recording in that the muscle potentials produced due to biting can distort the recorded evoked response (Goff et al 1969). The bite bar maybe substituted by a chin and head rest but the problem of patient fixation is still present. The Maxwellian view system is, therefore, not very practical in a clinical setting and for most experimental work.

A photostimulator placed in front of the subject or patient at 33 cms provides an adequate form of stimulation for luminance VERs. The amount of light entering the eye is not as closely controlled as in a Maxwelian view system as there is no control on pupil

size. The pupil size may be controlled by means of drug induced dilation and artificial pupils, however, the work of Skalka and Holman (1986) showed that this is not necessary. They looked at the effect of pupil dilation on the latency and amplitude of the responses recorded to flash stimulation. Pupil dilation did not produce a definite shortening in latency or alter the amplitude of the response recorded. Other workers have also come to the conclusion that pupil diameter and iris pigmentation are not important factors in the recording of flash VERs (Kooi & Bagchi 1964, Spehlmann 1965, Thorpe Davis et al 1987).

The refractive state of the subject has been shown to have a significant effect upon the response recorded, when using patterned stimuli, but does not significantly alter the response to a flash of light (Kooi & Bagchi 1964, Spehlmann 1965, Dustman & Beck 1969, Dustman et al 1977, Wright 1983).

The rate of stimulation will effect the morphology of the response recorded. If the stimulation rate of the photostimulator is less than around 2 per second the individual components of the flash VER, as described above, can be identified. This is termed a transient waveform. When the rate of stimulation exceeds this rate then the components merge together to give a more oscillatory response in which the individual components are not distinguishable. This is termed a steady state response (American EEG Society 1984).

Besides the rate of stimulation, the intensity of the flash has an effect on the response recorded. In studies in which the intensity of the flash was reduced from an initial starting level until absolute threshold was reached, an increase in the latency of the major positive component P2 was recorded with decreasing intensity of stimulation (Vaughan 1966). Vaughan (1966) used a starting intensity of 2.5×10^7 mL. A 6 log unit attenuation was required before an increase in the latency of the P2 component was demonstrated. In studies which have looked at a reduction in the intensity of stimulation

in relation to a clinical situation (Thorpe Davis et al1987) no increase in the latency of the P2 component has been observed, whilst the intensity of stimulation is still above retinal threshold. The reverse is also true as the intensity of stimulation is increased from threshold there is an initial shortening in the latency of the P2 component. However, after a certain level of intensity is achieved there is no further reduction in the latency of the P2 component (Whittaker & Siegfried 1983).

The effect of an increase in the intensity of stimulation on the amplitude of the response recorded varies from individual to individual. Some subjects show a reduction in amplitude and they are called 'reducers', whereas others show an increase in amplitude and they are called 'augmenters'. Dustman et al (1982) found that whilst adults tend to be augmenters children tend to be reducers. They postulated that the phenomenom of reducing or augmenting a response is a protective mechanism of the brain. Similar results have been shown by Cohn et al (1985) who found children aged 4-6 years were reducers.

3.3.0. THE EFFECT OF AGE AND MATURATION ON THE COMPONENTS OF THE FLASH VER.

3.3.1. THE EFFECT ON THE LATENCY OF THE RESPONSE.

It has been shown that the age of the subject affects the morphology of the waveform recorded from the occiput to a flash of light. This is not unexpected as the EEG is known to change from childhood through adulthood to old age (Duffy et al 1984). Background EEG activity in the elderly shows a reduction in slow activity and an augmentation of fast activity, with the greatest changes taking place in the temporal lobes.

Ellingson (1970) recorded flash VERs from six newborn full term babies and although the amplitude results were variable, the P2 component was present in all subjects. Other studies with young children up to six years of age have shown that the latency of all components reduces as the age of the child increases (Blom et al 1980, Barnet et al 1980).

Wright et al (1985) looked specifically at the influence of age on the flash VER in 70 subjects ranging in age from early teens to late seventies. Throughout the age range a P2 component was consistently recorded, whereas the later components were more variable. However, they found that the incidence of the P1 component was related to the age of the subject being more consistently recorded as the age of the subject increased. The latency of the P2 component was affected by the age of the subject showing a mean increase from 114.5 msec in the 10-19 age group to134.25 msec in the 70-79 age group. They found that the aging effects were common both to male and females so that the reported differences between sexes did not affect their results.
They postulated that the P1 component was not absent in the younger age groups but was obscured by high amplitude signals from extrafoveal areas. They also thought that the increase in the latency of the P2 component with age was not related to pupil size or a reduction in luminance of the stimulus, but was as a consequence of neural factors.

The gender of the subject does not effect the latency of the response recorded (Buchsbaum et al 1974).

3.3.2. THE EFFECT ON THE AMPLITUDE OF THE RESPONSE.

Dutsman & Beck (1966) studied 215 subjects from the age of 1 month to 81 years of age and looked at the amplitude of the response recorded to flash stimulation. They found that in the first six years of life there was an increase in the amplitude of the

response, followed by a decrease until the age of 15, after which the amplitude of the response was not significantly altered. The older groups, those in their 60s and 70s, showed an increase in the amplitude of the early components (0-125 msec) as the amplitude of the later components decreased (126-250 msec). In agreement with Kooi & Bagchi (1964) this was not thought to be related to pupilary size differences. Harding (1982) found in a normal population, with an age range of 6 years to 75 years, that the P1 component almost equalled the P2 component in amplitude in the older age group of 65-75 year olds.

The variability in the flash VER has been shown to reduce as children approach the age of 15, the age at which the adult VER appears to stabilise (Callaway & Halliday 1973).

A larger life span and twin study was undertaken by Dustman et al (1977) of 425 normal subjects whose ages ranged over 85 years. As previously reported (Dustman & Beck 1966) a rapid increase in amplitude of the response was found until the ages of 6-8 years. This was followed by a reduction in amplitude until the age of 13-14 years, after which there was a small increase to 16 years of age and then the amplitude values stabilised. The finding that the early components in the older subjects were larger than those in the young was confirmed, and this transition was thought to take place at around 35-40 years of age. The increase in the amplitude of the early components with age has been reported by later workers (Cosi et al 1982, Wright et al 1985). Dustman et al (1977) also showed that the amplitude of the response was greater recorded from the right hemisphere and in females than males. The differences between the sexes had also been reported by others (Buchsbaum et al 1974).

Wright et al (1985) found that the amplitude of the flash VER was 2-3 times greater for subjects in the 10-19 age group than in any other age group up to 80 years of age.

3.4.0. THE TOPOGRAPHY OF THE COMPONENTS OF THE FLASH VER.

3.4.1. AN HISTORICAL REVIEW OF THE MAPPING OF BRAIN ACTIVITY.

The concept of mapping the brain's activity is not new, Brazier in 1949 was addressing her research in this direction. She demonstrated a method of displaying the EEG, from sleeping subjects, in the form of electric fields and related it to dipole-like fields.

Walter & Shipton (1951) described a new version of an instrument they had devised to provide a topographic representation of the brain's electrical activity, which proved to be the forerunner of modern day brain mapping systems. In the original 'toposcope' the output from the electrodes were switched to a grid of a 12 inch cathode ray tube. Deflection voltages were applied to the cathode ray tube plates so that the spot occupied the same position on the outline of the head drawn on the screen of the cathode ray tube as the electrodes on the head. In the new version each of the 22 channels was connected to its own cathode ray tube the brilliance of which was modified by the amplified signals. The tubes were placed to represent a plan view of the head. The frequency and phase were directly indicated on the apparatus, this being achieved by means of a radial time base common to all tubes and rotated by means of a simple servo-mechanism. If the speed of rotation coincided with any multiple of frequency of signal a stationary pattern results. The frequency was determined from a knowledge of the rotational speed of the servo-shaft and an instantaneous dead-heat type of tachometer was incorporated. The time relations between signals in different channels could thus be directly observed.

In 1965 Rémond suggested a technique to overcome the problem of presenting a series of topograms each at a specific point in time, he suggested the chronotopogram.

The idea was to enable the observer to see how the potential gradient evolved over time (Figure 3.4). The scale along the bottom is of time and the scale at the side is the potential recorded at the illustrated electrodes. The black shading represents potential of negative amplitude whilst the white shading represents potential of positive amplitude. The resultant map was very complicated and was not taken up widely as a method of data presentation.

3.4.2. TOPOGRAPHICAL INVESTIGATION OF THE FLASH VER BY MEANS OF SCALP ELECTRODES.

After the work to localise activity in the EEG it was only a matter of time before the same techniques were applied to localise visually evoked activity.

Lehmann et al (1969) investigated a patient who had suffered a traumatic split of the chiasma resulting in a bitemporal hemianopia with a straight vertical boundary through the centre of the fovea. Monocular flash VERs were recorded from occipital and parietal electrodes placed 10 and 3 cm in front and 5 cm lateral to the inion over both hemispheres. The response recorded showed a wave with a major peak at around 140 msec, which was positive on the ipsilateral occipital electrode, referred to the ipsilateral parietal electrode, but was of smaller amplitude and of inverted polarity when recorded from equivalent positions over the contralateral hemisphere. They calculated that a single source of electrical activity in the ipsilateral cortex to the stimulated eye accounted for almost all the evoked response. A second minor source may be active after 160 msec after the flash.

Bourne et al in 1971 used bipolar recording techniques to look at the topography of the flash VER recorded from 17 electrodes, four electrodes per run, concentrated over the occipital region. They displayed their data by means of a grey scale, and showed a

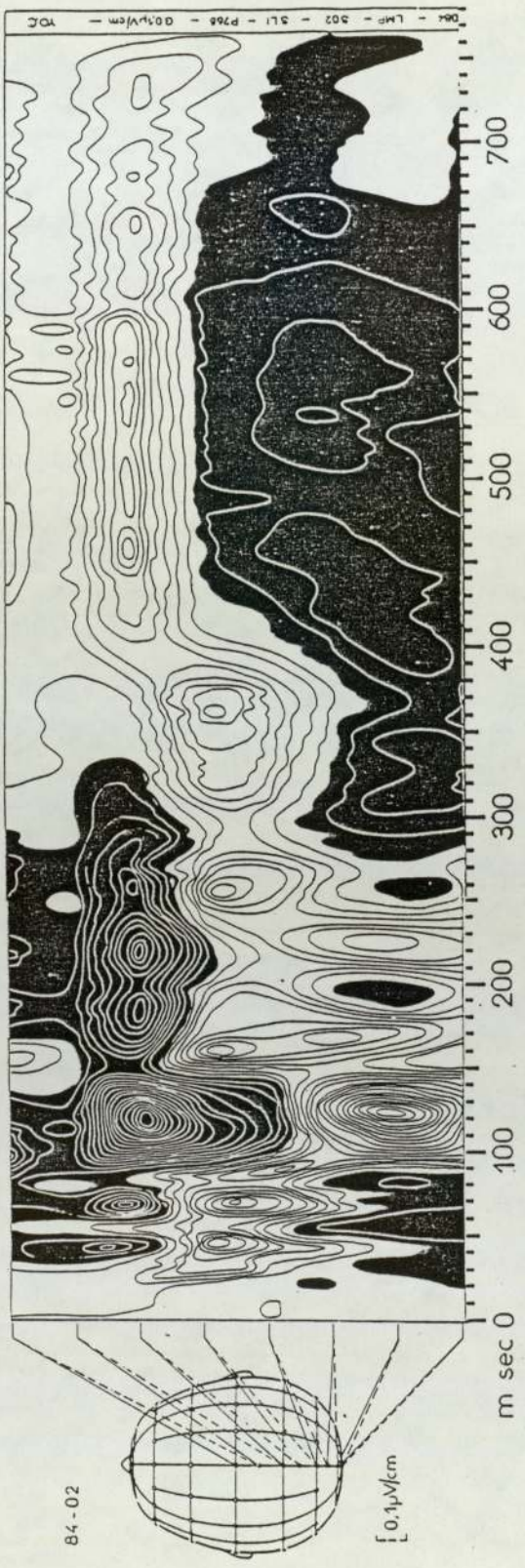


Figure 3.4:- after Rémond (1965) a spatiotemporal map of the VER scalp distribution.

potential spread rotating over the occipital area. The potential initially had an upward slope from the inion anteriorly, and then, as the VER developed, it maximised itself over the inion. They proposed that the early part of the response, before the first 120 msec, had a source anterior to the occipital region, whereas the second phase at 190-310 msec had a source within the occipital area.

Nakamura & Biersdorf (1971) investigated the topography of the early components, i.e. those before 100 msec, of the flash VER. They attempted half field stimulation using red light. The subject sat in a brightly illuminated hemisphere which had an aperture that could be half occluded to provide half field stimulation. They recorded both full and half field responses from electrodes placed at P3, P4, Pz and Oz referred to linked earlobes. They found that the P1 component was recorded maximally over the Pz electrode and on half field stimulation was located over the hemisphere receiving the primary projection. The P2 component did not show this lateralisation to half field stimulation and was located nearer to the midline. Lehman et al (1969) failed to find half field localisation and this was thought to be due to the fact that they used white light and that their experiment suffered from stray light effects.

In 1972 Biersdorf & Nakamura extended their work to include patterned flash. Using light adapted subjects, they found lateralisation with half fields. The results compared well with the previous blank flash study, the main difference being that the waveform with the blank flash was more complex. The contour maps for both blank and patterned flash VERs were similar showing tangential dipoles located over the contralateral hemisphere in the primary visual cortex.

Allison et al (1977) identified twenty two components of the flash VER recorded from 24 electrodes referred to the contralateral earlobe. The frontal N20, P50 and P65 components were thought to be the a-wave, x-wave and b-wave of the electroretinogram (ERG). They found larger frontal negative potentials in naive subjects

and that predictable stimuli produced smaller frontal potentials than unpredictable ones. Similar potentials to the surface occipital potentials P40, N70, P80 and P95 could be recorded from occipital depth electrodes suggesting that the major part of the scalp flash VER is neurogenic.

Hoeppner et al (1984) recorded flash and binocular pattern reversal VERs on three patients who had undergone unilateral occipital lobectomies, with no resultant shift in their anatomical midline after surgery. The electrodes were placed in accordance with the electrode placement of Halliday et al (1977a) and referential recordings, to a midfrontal reference, were made. The flash responses to full field stimulation were similar to the pattern reversal responses in as much as they were of normal amplitude and latency over the ablated hemisphere and distorted over the intact hemisphere. This phenomenon was not attributable to the reference site chosen or restricted to electrode position as the same results were obtained for two of the subjects using the O1-A1, O2-A2 configuration. These results confirm the findings for pattern reversal stimulation (Barrett et al 1976, Blumhardt et al 1978), thus indicating that the generators of the flash VER are tangentially orientated in the cortex and are maximally detected over the contralateral hemisphere. It should be remembered, however, that in this study the patients had undergone major surgery and would have large fluid filled spaces, in place of their occipital lobes, which could have an effect on volume conduction.

3.4.3. MAPPING OF VISUAL EVOKED RESPONSES.

In 1978 Ragot & Rémond described a method for the plotting of isopotential maps of brain activity for EEG work and evoked potentials. Recordings were made from 48 electrodes and maps were created by calculating the electrical potential at each point on the scalp for each time interval by means of second order interpolation methods. The maps presented were of the potential distribution at selected points in time. The use of

48 electrodes resulted in a 4 cm inter-electrode distance. They felt a 2 cm inter-electrode distance would be preferable, however, this would require the use of 200 electrodes.

The system devised by Duffy et al (1979) used recordings from 24 scalp electrodes and can be applied to either EEG or evoked potential work. Three types of data analysis were possible; firstly spectral analysis can be performed on the background EEG by means of fast Fourier analysis. Secondly the average evoked potential voltage of 128 epochs each lasting 4 msec can be determined for each electrode and stored for later display. Thirdly the raw EEG containing spikes can be digitised. The data is displayed in colour on an outline of the head. For areas on the scalp that are not the actual location of the 24 electrodes are filled by linear 3-D interpolation based on values of the three nearest neighbours. The data the system is able to display is the spectral energy in any EEG band, the evoked potential voltage at any 4 msec epoch after stimulus onset, EEG amplitude at the peak of a spike and statistical analysis on any of the above.

Buchsbaum et al (1982) described a method by which the distribution of the brain's electrical activity could be presented as a grey scale plot over the surface of the scalp. They developed the system recording from sixteen electrode sites placed according to the 10-20 system. To create the grey scale maps a four nearest neighbour interpolation algorithm was used with a weighting system to take into account the position of the picture element from each of the four electrodes. The result was an easily interpreted contour plot of the brain's activity.

Duffy (1982) described the clinical applications of their brain electrical activity mapping (BEAM) system for evoked potential work. They found that the flash stimulation activates the cortex more widely than pattern reversal stimulation does. They thought their system had the following advantages, 1) mapping presents spatial information in a more concise form, 2) the ability to cartoon through the data enables spatio-temporal

patterns of brain activity to be more easily perceived. They also introduced significance probability mapping and grid sector analysis which would improve the clinicians ability to distinguish between normal and abnormal.

Thickbroom et al (1984a) mapped the evoked potential of a half field pattern reversal response using their mapping system. The method they described required the use of 30 electrodes placed in the standard 10-20 locations. They projected the electrode positions on the head onto a flat two-dimensional outline of the head. The Cz electrode was marked first in the centre of the of the outline and the other electrode postions calculated from it. A 32 x 32 grid was superimposed onto the head outline and the projected electrode positions equated with the nearest grid site. The voltages at the positions on the grid which did not correspond to an electrode location were interpolated. Interpolation was by means of Buchsbaum et al's (1982) four nearest neighbour electrode method. The map was presented in an eight colour scale. They mapped a left half field pattern reversal response referred to a sterno-clavicular reference and then transformed it to an average reference in order to reduce low frequency reference contamination. They found that the potential field was approximately dipolar. When they recorded the same field using the standard twenty electrode 10-20 system montage they found that the map was very similar, but had a slightly reduced definition.

The systems described above have all been based on linear interpolation methods to create the spatio-temporal maps. Perrin et al (1987) described a method of interpolation, called 'surface spline interpolation', which they claim gives smoother maps and locates extrema more precisely. Their method was originally invented for the design of air craft wings. They compared the four nearest neighbour and surface spline methods on a simulated evoked potential generated by using a current dipole within a spherical conductor. They concluded that the chief advantage of the surface spline method was that it allowed the use of irregularly placed electrodes. The extrema of the

potential are not necessarily located over an electrode site and the surface spline method in general gave a better estimate of potential generation. The main disadvantage of this method of analysis is that it requires more computer time (for a detailed description of the mathematics see Perrin et al (1987)).

3.4.4. DIPOLE LOCALIZATION METHODS.

In 1982 Wood applied the dipole localization method (DLM) to source identification of human evoked potentials. DLM can be used on the following assumptions, firstly the head consists of three spheres brain, scalp and skull and that each region is homogenous. The brain and scalp are assumed to be of equal resistivity, with the skull being eighty times greater. Finally, the surface potential field is assumed, at any time, to approximate to that generated by a dipole source. It is not suggested that evoked potentials are generated by physical dipoles, but that the concept of an equivalent dipole is the best way of describing the potential field generated by a number of sources and sinks. Based on these assumptions the DLM method fits the best dipole for a given surface potential. The equation used to calculate the surface field generated by a dipole, in a spherical medium, has six parameters; X, Y, and Z coordinate locations and dipole moment or strength parameters along the X, Y, and Z axes. The initial values for the six parameters are arbitarily chosen, the resultant field is generated for that dipole, and compared to the recorded field. The parameters are then changed and the process is repeated until as close a match as possible is achieved. They applied this technique to pattern reversal stimulation, but not for flash stimulation, and found that the best fitting dipole for right half field stimulation is near the midline in the left hemisphere and near the midline in the right hemisphere for the left half field. In both cases the dipoles are pointing to the opposite hemisphere. Thus, DLM only shows whether the evoked potential field recorded approximates to a dipole field.

The work above had been preceded by the development of equivalent dipole techniques during the early seventies (Schneider 1972, Henderson et al 1975).

3.4.5. CURRENT SOURCE DENSITY ANALYSIS (CSD).

A method of analysing the potential fields recorded from intracortical electrodes is that of current source density (CSD). The transmembrane currents which flow across the membrane of active neuronal cells form a series of sources and sinks with respect to the extracellular medium. The extracellular current flowing between the sinks and sources results in a potential difference being set up which is the recorded potential field. CSD is a scalar quantity which measures the amplitude of the source or sink of current at a given point (Nicholson & Freeman 1974).

The monkey flash VER is very similar to the response recorded in humans although it tends not to show the alpha like afterdischarge seen in man (Vaughan & Gross 1969, Creel et al 1973). Snyder et al (1979) showed that the flash VERs recorded from macaque monkeys were comparable within individuals and repeatable over time. Besides the work carried out on humans the generators of the flash VER have been investigated in the monkey using CSD analysis.

Mitzdorf & Singer (1979) investigated the potential field distributions in areas 17 and 18 of the visual cortex of the macaque as a result of electrical stimulation of the primary afferents. They concluded that the early sinks discovered were as a result of monosynaptic activity and that later sinks were as a result of polysynaptic or intracortically mediated activity. They could also confirm (as described in Chapter 2) that the afferents from the magnocellular layers of the LGN terminate in layer IVcα and the afferents from the parvocellular layers terminate in layer IVcβ. It would also appear that the most obvious disynaptic connections are made within these two layers, whilst trisynaptic

activity is thought to take place within layer Va, as a result of the disynaptic activity in layer IVcβ. Investigation of area 18 revealed that the parvo- and magnocellular afferents project to layer IV from area 17.

Kraut et al (1985) investigated the generators of the flash VER in five macaca monkeys by means of sixteen intracortical electrodes. They investigated the generator sites of the flash VER in three different ways. One was to record the intracortical distribution of the VER and relate it to the components recorded at the scalp. Secondly they used current source density (CSD) analysis to estimate the laminar pattern of transmembrane current flow. Thirdly they used multiple unit activity (MUA) analysis, which allows investigation of the spatio-temporal patterns of neural firing associated with changes in CSD. In the monkey they recorded a surface positive component at around 65 msec (P65) which they thought was equivalent to the P100 or the P2 component in humans. They found that this wave reversed in polarity as various layers of the cortex were breached and became a negative potential with a latency of 80 msec in lamina IVcβ. These complex changes within the cortex reflect the combination of various sources and sinks at different cortical layers. The MUA of the P65 component showed that it is a reduction in firing in lamina IVa and IVc. The CSD profile showed a large source in lamina IVcβ during the 60-110 msec time span. They argued that the P65 component represents inhibitory postsynaptic potentials (IPSP) in cortical elements. The reduction in the MUA appears to reflect the postsynaptic inhibition of neurons within lamina IVcβ. As the thalamic-cortical input does not last beyond 60 msec it is highly unlikely the the inhibitory input comes from the LGN and that the P65 represents intracortically generated inhibition in lamina IVcβ. By looking in a similar way to the components which preceded the P65 component they postulated that the sequential depolarization and hyperpolarisation of the stellate cells within lamina IVcβ generated the prominent N40 and P65 components of the flash VER. This would also indicate that the flash VER is

the result of stimulation of the parvocellular cells of the LGN as they terminate in lamina IVcβ (Hubel & Wiesel 1972, Lund et al 1979, Blasdel & Lund 1983, Blasdel & Fitzpatrick 1984).

3.4.6. SOURCE DERIVATION METHODS.

Hjorth (1975, 1980) described a technique, termed 'source derivation', for localising the source of potentials at the scalp recorded by an EEG. It is a method to identify the sinks and sources present in scalp flow which correspond with the maximum current flow in and out of the cortex, by measuring the potential gradient directed at a particular electrode from those electrodes surrounding it. They introduced a correction factor to the electrodes at the edge of the 10-20 montage to account for the fact that these electrodes did not have contributing electrodes below them. The major advantage of source derivation is its ability to eliminate any potentials originating from outside the recording area.

Thickbroom et al (1984b) applied the source derivation techniques to the localisation of pattern VER generators. They recorded left half field pattern stimulation from thirty electrode sites, referred to a balanced non-cephalic reference, on seven male volunteers. They applied the technique of Hjorth (1975) for each electrode i.e. the weighted average of the waveforms from all the other electrodes was subtracted from the waveform at each electrode in turn, the weighting being calculated as a relationship of the distance of the electrodes from the electrode at which the transformation is taking place. They concluded that source derivation produced waveforms which are not influenced by the reference site and may provide a more accurate picture of the electrical activity taking place.

The method of source derivation described by Clement et al (1985) was applied to pattern reversal evoked potentials by Flanagan & Harding (1986). They found that the source of the pattern reversal potential was situated at Oz for both right and left half field stimulation and it was the orientation of the associated sink that was altered by the stimulation of different half fields.

Their method of source derivation is also based upon that of Hjorth (1975), but they used a chain of electrodes. To calculate the source derivation from the scalp distribution recorded using a common reference, the distribution must be differentiated twice. This can either be done computationaly or by recording the bipolar distribution and then recording the bipolar of the bipolar distribution. The resulting distribution being the source derivation. The limitation of this method is that successive bipolar recording results in the loss of the electrodes at the end of the chain i.e. from an initial recording chain of seven electrodes the source derivation would result from the inner five electrodes. They felt source derivation was complementary to dipole modeling.

3.4.7. POSITRON EMISSION TOPOGRAPHIC INVESTIGATION OF EVOKED POTENTIALS.

Positron emission tomography (PET) measures the localised metabolic rate of neuronal structures and regional blood flow. These two measures increase when brain activity is increased. Phelps et al (1981) used PET to investigate which areas of the visual cortex are activated by different stimuli. They looked at a flash of light, checkerboard patterns and the effect of looking at more complex visual scences. They concluded that for white unstructured light stimulation most of the activity was confined to the area 17 with slight activation of areas 18 and 19, as the visual task became more complicated areas 18 and 19 became more involved. Celesia et al (1982) used PET to investigate the site of visual response generators. They used both flash and pattern stimulation on patients with

homonymous hemianopias and one cortically blind man. They found that stimulation with either flash or pattern reversal targets produced an increase in regional cerebral blood flow in areas 17, 18 and 19 equally, a contrary finding to Phelps et al (1981). They did agree with Phelps et al (1981) however, that the viewing of a complex pattern rather than a simple pattern resulted in a greater increase in activity in areas 18 and 19. They concluded that the surface potentials recorded at the scalp reflect the interactions of three cortical areas rather than sole volume transmission of striate dipoles. They postulated that a small area of cortex is sufficient to generate a VER and depending on its location it is either insufficient for conscious visual perception or capable of producing basic visual perception only.

3.4.8. NEUROMAGNETIC EVOKED FIELDS.

A different method for the localisation of cerebral generators of evoked potentials is to record their neuromagnetic fields. The advantage of this method is that low frequency magnetic fields, less than 1 kHz, are hardly affected by neural tissue and leave the head undistorted. Neuromagnetic fields are recorded by placing a superconducting coil in a Dewar flask filled with liquid helium. The Dewar is then placed at a set distance from the scalp the coil being kept tangential to the scalp. Stimulation is provided for the appropriate modality and the response is filtered and averaged. The position of the Dewar is altered 1cm at a time until a response is recorded above the background noise. The position of the Dewar is moved in very small steps until the whole region of the head from which a similar response can be recorded is determined. On completion of this the Dewar is moved to determine the region of head from which a response of opposite sign can be recorded. This area is then painstakingly determined and a contour map drawn showing the loci of fields of equal strength. The maxima recorded by electrical means are along the axis of the source whereas the maxima measured by magnetic means are at right angles to the source. Unlike electrical field potentials the depth of the source

can be calculated from neuromagnetic fields. It is possible to compute the depth of a source from the radius of the head, calculated by measuring its curvature, and from the distance along the scalp separating the extrema having first made the assumption that the head is a sphere (Kaufman & Williamson 1982). In recent years it has become possible to record from up to 14 channels (Kaufman & Williamson 1987).

3.5.0. COMPARISON OF SCALP AND INTRACORTICAL RECORDINGS OF THE FLASH VER.

Ducati et al (1988) recorded both surface and intracerebral flash and pattern reversal evoked potentials from four awake patients who were undergoing sterotactic procedures for dyskinetic disorders. Flash stimulation was presented at 1Hz, the click was masked, and the responses were referred to the shoulder on the unaffected side. Intracerebral VERs were recorded at 5-10 mm steps and skull X-rays were taken to identify the depth to which the surface had been pierced. They found that the morphology of the surface and intracerebral waveforms was different, the main effect being an inversion in polarity of components. They postulated that this may be due to the fact that the intracerebral electrode only picks up activity directly under its tip and is not affected by activity from other parts of the cortex. In addition a subdural recording will not be influenced by the filtering effects of bone and skin. The polarity inversion was observed as soon as the electrode passed beneath the cortex which indicated that the generator of the surface potential was within the cortex. They found that the P1 component of the flash VER was generated nearer the surface of the cortex than the P2 component. Waves recorded deep within the cortex i.e. 65 mm were not recordable at the scalp. They made recordings from the rostral extension of the striate cortex, on which the peripheral parts of the retina are mapped. The latency of the response recorded had an onset of 30 msec and was thought to represent peripheral retinal

activity. They suggested this might represent Y-system activity in the flash response. Kraut et al (1985), from their work on monkeys, had postulated that the flash VER was the result of parvocellular activity (X-system). Ducati et al (1988) did not disagree that the X-system may generate the flash response recorded at the scalp, but felt that intracerebral and scalp recordings could be affected differently by X- and Y-system input. The inversion of the pattern reversal response they recorded as the electrode crossed the cortex implies that the generator of all surface components of the pattern reversal VER is the striate and parastriate cortex.

It should however, be remembered that all non-invasive techniques can only approximate to the anatomical site of any evoked potential and that invasive techniques, such as intracortical electrodes, are only accurate for the individual from which the recording is made. Brindley (1972) dissected fourteen human brains and showed that although they were all very similar they were not anatomically identical. Schwartz et al (1984) by use of positron emmission tomography examined the human visual cortex and concluded that the borders of the striate cortex may vary quite considerably between individuals. Stensaas et al (1974) examined 52 hemispheres in autopsied human brains and compared the striate regions. They found that between 60-70% of the striate cortex is within the calcarine fissure, its branches and other sulci with most of the exposed striate being on the mesial surface. The actual area of striate cortex varied considerably from 1284 to 3702 mm^2 and the area of exposed striate cortex varied from 359 to 1308 mm^2.

However, despite the limitations expressed above visual evoked potentials remain a very useful research tool for the investigation of the workings of the human visual system.

3.6.0. THE CLINICAL USES OF THE FLASH VER.

The value of any electrophysiological technique can be twofold. Firstly as a research tool to investigate the workings of the brain and its afferent pathways and secondly in a clinical setting as an aid to diagnosis. VERs can be used to assess the condition of the central retina, optic nerve, optic tracts and the visual cortex. Flash stimulation is often used in conjunction with pattern stimulation in the assessment of visual function.

Pattern stimulation can take the form of either pattern reversal or pattern onset/offset. In pattern reversal stimulation the checkerboard is ever present and the stimulation is provided by the black and white elements of the pattern changing places. In pattern onset/offset the pattern abruptly appears and then after a set period of time abruptly disappears, to be replaced by a blank screen of equal average luminance. The response recorded to pattern reversal stimulation is a simple waveform with a single major positive component at about 100 msec (Figure 3.5). The pattern onset/offset response, on the other hand, consists of three components, a positive CI component, a negative CII component, and a positive CIII component and these are followed by the offset response (Figure 3.5). The CII and the CIII components are thought to be the contour response i.e. the cortex's response to the edges and angles of the pattern, whilst the CI component is the response to the changes in contrast. The pattern reversal response, on the other hand, is thought to be a contrast response, as the checks are ever present it is thought that the cortex adapts to the contours of the pattern. On the whole pattern reversal stimulation is the more widely used clinical tool.

Flash and pattern stimulation provide complementary information which when viewed together provide strong diagnostic information. A limitation of pattern stimulation is that it requires the patient to have sufficient visual acuity to see the pattern clearly whereas flash stimulation requires no such acuity levels. The co-operation and attention of the patient are also necessary for pattern stimulation.

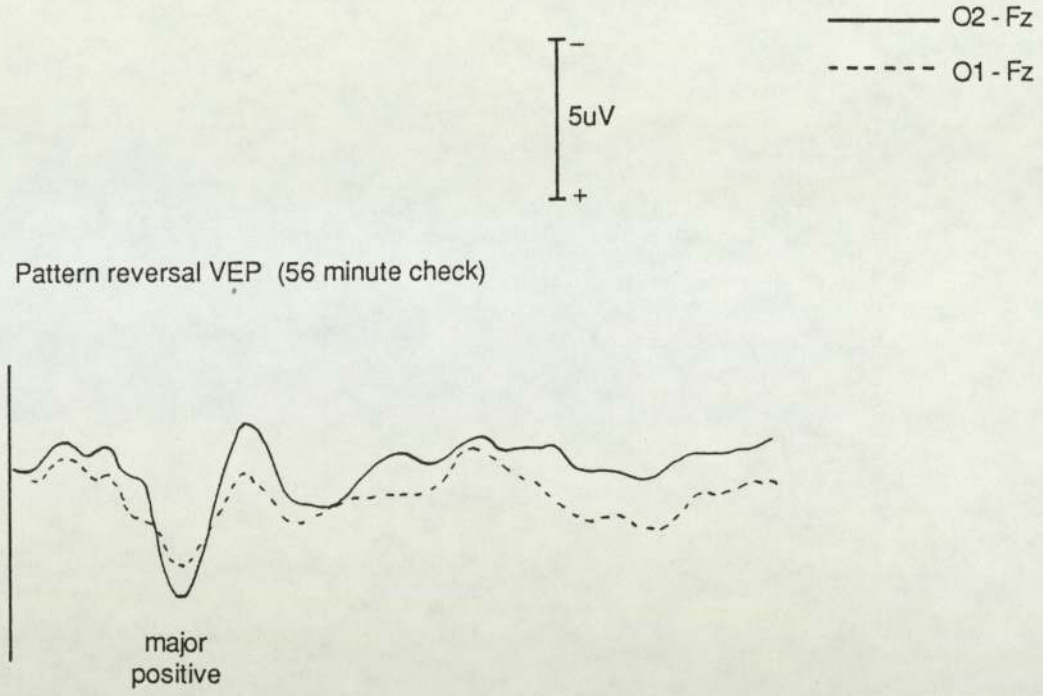


Figure 3.5:- An example of a normal pattern reversal and pattern onset/offset VEP (after Wright et al 1985)

Flash stimulation is the sole form of visual stimulation for evoked potential recording in cases where there is a gross reduction in visual acuity for e.g. dense cataract, vitreous haemorrhage, major eye injury or where there is a lack of patient co-operation for e.g. malingerers. It is commonly used in conjuction with pattern reversal stimulation for the investigation of other ocular and medical conditions such as retrobulbar neuritis, retinal dystrophies, space occuping lesions, toxic conditions and Alzheimer's disease. A brief description of the responses recorded in a variety of conditions are given below.

Flash VERs are recorded to investigate lesions of the optic nerves and tracts. Although the intra-subject variability of the flash response is greater than for patterned stimuli the inter-subject variability is small, especially between hemispheres, therefore uniocular stimulation and analysis of hemispheric symmetry is a clinical requirement. The reduction in amplitude or absence of a VER from one eye compared to the other would indicate either dysfunction in the optic nerve fibres or complete optic nerve damage from that eye. Besides trauma, the optic nerve can be affected by toxic or degenerative conditions. It has been shown by Harding & Crews (1982) that in hereditary optic atrophy the flash VER takes on a different morphology from that normally recorded. The response they recorded showed a positive-negative-positive (PNP) configuration, the latency of the negative component being about 100 msec. These results were not associated with visual field defects. Post-chiasmic lesions show as a reduction in the amplitude of the response over one hemisphere which is consistent which ever eye is stimulated. An amplitude difference between hemispheres of as much as 50% is not uncommon in normal subjects (Borda 1977).

Vaughan et al (1963) proposed the use of the flash VER for the assessment of homonymous visual field defects in cases where patient participation or co-operation could not be relied on. They suggested that a significant level of hemispheric asymmetry was 50%. They found when using a midoccipital reference that it was difficult to distinguish the abnormal side from the normal side in patients with field defects. To

overcome this problem Harding et al (1969) devised a montage to locate the hemisphere of evoked potential generation for visual field investigation. This is described more fully in section 3.2.2.

The amplitude of the P2 component of the flash VER can be used as a predictor of post-operative visual acuity in the case of patients with cataract (Thompson & Harding 1978). The response recorded from the eye with the cataract was graded compared to the response from the normal eye or an age matched normal value. A response of normal amplitude was a Grade I response, a reduction in amplitude of less than 50% was a Grade II response and a reduction in amplitude of greater than 50% was labelled as a Grade III response. Their results showed that a Grade I response resulted in a post-operative visual acuity of 6/12 or better, whereas a Grade III response was associated with a post-operative acuity of 6/24 or worse. No diagnostic value was found in the latency values recorded between the eyes. The P2 component was used, as it was the component which showed least variability, was not affected by the age of the patient, and was most predictive of post-operative outcome.

Crews et al (1978) modified the grading system of Thompson & Harding (1978) to predict the visual outcome of patients with major eye injuries. In this study they found that the latency of the flash response recorded from the injured eye was a significant factor and the responses recorded were classified into one of four grades. A Grade I response had a normal latency and amplitude compared to the normal eye or an age matched eye. A Grade II response had a less than 50% reduction in amplitude and no marked delay. A Grade III response was reduced in amplitude by more than 50% and was delayed by more than 30 msec from the normal range. Finally, a Grade IV response was an absent response or greatly reduced, less than 1.5 μV, and delayed at the highest intensity stimulus. Electroretinograms (ERG) were also recorded and were put into one of three categories on the basis of the amplitude of the b-wave. A Grade I ERG has a b-wave of 75-100% of normal amplitude, a Grade II ERG has a b-wave of 50-74% of

normal amplitude and a Grade III ERG has a b-wave of 25-49% of normal amplitude. Based solely on the VER predictions 67% of patients with Grade I or II VERs achieved a visual acuity of 6/60 or better. They found that if they combined the patient's VER and ERG scores together then the diagnostic acumen of the test improved. It was found that 90% of eyes with visual potential had a combined score of 2-4, whereas 91% of eyes with no visual potential had a combined score of 5-8. This study shows the value of the flash VER either in isolation or in combination with the flash ERG when a pattern stimulus would provide no or very little information.

A loss of the early components and the P2 component can reflect macular problems, as the VER reflects activation of fibres mainly from the central retinal area i.e. the central 8-10° (Borda 1977). The ERG in these conditions is usually perfectly normal which is opposite to the case of retinitis pigmentosa where an abnormal ERG is accompanied by a normal flash VER.

The role of the visual evoked potential in the diagnosis of optic neuritis is well established (Halliday et al 1972). The condition is characterised by a normal flash P2 latency and a delayed P100 pattern reversal component and even when the acuity has returned to normal the pattern reversal response still shows a marked delay. The amplitude of the flash visual evoked potential is greatly reduced during an acute attack of optic neuritis and the response can be abolished completely if the vision is reduced to perception of light returning to normal as the vision improves (Ellenberger & Zeigler 1977, Halliday & Mushin 1980) Changes in latency of the flash visual evoked potential are rarely sufficiently large or clear cut to allow a distinction between normal and abnormal in individual subjects. Halliday et al (1977b) did not find any correlation between the level of acuity and the magnitude of the delay in the P100 component of the pattern reversal response i.e. an eye with normal visual acuity could give delayed pattern responses. They thought the amount of delay may depend upon the length of demylinated fibres in the plaque, whereas the recovery in amplitude maybe a reflection of the restoration of

conduction as the odema subsides in the initially blocked nerve fibres. In 1972, Halliday et al had suggested that the delay in the pattern reversal response may be a reflection of the vulnerability of the macular fibres to demylination whilst the flash VER is reflecting the integrity of fibres from a larger area of the retina. Wright et al (1984a) who, besides recording pattern reversal, pattern onset/offset and flash VERs, recorded the contrast sensitivity function of patients with unilateral retrobulbar neuritis did not agree with this suggestion. They concluded that all fibres involved in the transmission of spatial information were affected and there was no relationship between the fibres affected and the area of retina.

In 1969 Unoyama et al had looked at the effect of raised intraocular pressure (IOP) upon the flash VER of the cat. They found that all responses gradually disappeared as the IOP was raised to the level of systolic blood pressure. The decreasing amplitude being most marked from the optic tract, then the LGN and lastly the response from the visual cortex. Bartl et al (1974) looked at the effect of elevated IOP on the ERG and the VER in humans and correlated this to blood supply of the retina and the optic disc. They found a decrease in the flash VER amplitude when the IOP was 20% above diastolic blood pressure and as the IOP approached systolic blood pressure of the ophthalmic artery the VERs were abolished completely.

Most of the studies looking at the clinical application of VERs in the diagnosis of glaucoma have used patterned stimulation. This is based on the belief that glaucomatous damage is thought to affect retinal ganglion cells which are pattern specific. The overall conclusion is that glaucoma causes a delay in the P100 component of the pattern reversal response. There appears some controversy as to whether this delay is correlated to the size or location of a visual field defect (Galloway & Barber 1981, Huber & Wagner 1978, Levy & Korhnak 1978, Huber 1981, Towle et al 1983).

Research in recent years in the glaucoma field has been concerned with the use of the pattern electroretinogram (PERG) (Wanger & Persson 1985, Trick 1986, Drance et al 1987, Marx et al 1988).

One of the more recent papers has reverted back to flash stimulation, Good et al (1987) report a reduction in amplitude of the P1 component with the maintenance of a normal amplitude P2 component in patients suffering from chronic open angle glaucoma. This supports the work of Harding (1982). They regard an amplitude of 4 μV as a critical amplitude value, such that a P1 amplitude below this level is an indicator of nerve fibre loss due to glaucoma or ischaemic damage. This reduction in amplitude may be recorded before any measurable field loss. However, no information is provided as to the intensity of stimulation or the age of the patients. They suggest that the P1 and the P2 components of the flash VER have different origins. On the basis of their own data that P1 is preserved in cases of maculopathy and that in glaucoma the papillomacular nerve bundle is spared, they hypothesise that the P1 component is not derived from the macular area.

The role visual evoked potentials in the diagnosis of neurodegenerative disorders is not as well established. The use of visual evoked potentials to aid in the diagnosis of pre-senile or Alzheimer's disease has increased over the years. Harding et al (1981) and Wright et al (1984b) recorded both pattern reversal and flash VERs in patients suffering from dementia, the term pre-senile was applied if the patient was less than 70 years of age. They found a delayed P2 flash component and a normal P100 pattern reversal component in these patients. There was no significant difference in the amplitude of the responses recorded. Interestingly there was no increase in the latency of the P1 component of the flash VER in the patients suffering from dementia compared to the normal group. The results above confirm the findings of Visser et al (1976) and Cosi et al (1982). A delayed flash P2 component and a normal P100 component has also be shown to be of value in the diagnosis of multi-infarct dementias (Wright et al 1988).

Wright et al (1984b) proposed that as it is the association areas of the brain that are more commonly affected in Alzheimer's disease with the occipital cortex left unimpaired, perhaps P1 represents geniculo-calcarine input to the primary visual cortex, whereas P2 reflects integrity of higher cortical areas. A possible explanation for the delay in the P2 component in Alzheimer's disease is the reduction in the transmitter substance acetylcholine causing defects in neural transmission. Further work by Wright et al (1987) examining patients with Alzheimer's disease with pattern reversal and pattern onset/offset stimulation as well as flash stimulation has led them to the suggest that the P2 component of the flash VER may originate from area 19 of the cortex. This hypothesis is based on the recording of normal P100, P1 and CII components, which are thought to originate from areas 17 and 18, and the delayed P2 component.

3.7.0 THE FLASH VER AND CORTICAL BLINDNESS

There have been a few case reports as to the electrophysiological findings in patients who have been diagnosed as cortically blind. Some workers have reported the loss or reduction of the flash response, whereas others have reported the persistence of the flash response. Kooi & Sharbrough (1966) reported on a victim of a road traffic accident whose visual capability was of perception of light and movement but not of form or colour. Although, only a very small occipital surface positive was recordable at around 200 msec a well defined vertex sharp wave was recordable at around 195 msec. Bodis-Wollner (1977) used pattern evoked potentials to confirm a case of cortical blindness, the result of a vascular accident. A response to a grating pattern, even at very high contrast, could not be recorded at the time the patient claimed no vision. However, when the patient's vision improved and she reported being able to see the pattern, normal pattern evoked responses were recorded. No information was provided as to the areas of the brain affected or how extensive the insult was. In both cases normal pupil reactions and ocular motility to command were present.

Two cases of cortical blindness due to lesions of the occipital lobes were investigated by Brindley et al (1969) to try and ascertain the role of the non-geniculate fibres of the optic tract. The evidence of normal pupil reactions and ocular movements to command was strong evidence that the non-geniculate fibres were intact. In both cases the only visual function present was an ability to distinguish the sudden darkening of a bright room or the sudden lighting of a darkened room. The cause of visual loss in one case was due to infarction of both occipital lobes with extensive damage. Two years later the patient was re-examined and was found to have the same visual state i.e. an ability to distinguish a sudden darkening or lightening of a room but was still unable to distinguish a flashing light. They concluded that their work would support the hypothesis of Marquis (1934), that the non-geniculate fibres may have a visual function similar to but cruder than the geniculo-calcarine system, or the hypothesis of Sprague (1966) that the non-geniculate fibres collaborate with the geniculo-calcarine system in higher visual fuctions. Although, Sprague (1966) found an interaction between the cortex and the superior colliculus it should be noted that this work was performed in the cat and whether parallels can be drawn to man is unclear.

Bodis-Wollner et al (1977) investigated a six year old boy who had been blind since an acute febrile illness at the age of two years. He was unable to locate a bright light in a dark room and did not demonstrate a blink reflex to light or threatening movement. A CT scan showed preservation of area 17 and part of the optic radiation, however, there was complete destruction of areas 18 and 19 of the right hemisphere with some preservation of the areas of the left hemisphere. Electrophysiological investigation revealed essentially normal flash VERs and normal pattern reversal VERs to patterns of low spatial frequency. The flash VERs were of normal amplitude but were slightly delayed. They concluded from this case that, unlike animals, the visual association areas are essential for vision in man. In monkeys complete abalation of area 17 does not result in complete blindness (Humphrey & Weiskrantz 1967). The other explanation is that the destruction

of the boy's association areas occured during a critical period of their development whereas all animal studies are performed on adult animals.

Celesia et al (1980) investigated a 72 year old woman with destruction of area 17 but with preserved areas 18 and 19, as shown by CT scan. She had no perception of light, however her pupil reactions, ocular movements to command and her fundi were normal. Normal flash and pattern reversal VERs were recorded. After two years, she still had no perception of light and would suggest that in man there is no recovery in vision after extensive damage to area 17. This finding agreed with that of Brindley et al (1969). Celesia et al (1980) concluded that complete blindness results from the destruction of area 17 in man, although areas 18 and 19 may be preserved. They showed that pattern and flash VERs could be recorded when area 17 had been destroyed, that a VER could be recorded when vision is absent and finally, when there has been bilateral destruction of area 17, that VERs may be mediated via retinotectalcortical pathways. As shown in Chapter 2, it has been found in primates that there are retinotectal pathways to the SC which then projects to areas 17 and 18 via the pulvinar (Goldberg & Robinson 1978). However, from the above study it would appear that this secondary visual pathway, if it occurs, can not provided conscious visual perception in man.

The criticism that can be leveled at the studies described above is that of the correct identification of areas of destruction and whether that destruction is complete. The introduction of the CT scan has helped in this respect, however it is not possible to state beyond doubt the exact extent of anatomical damage. Two of the cases described above have shown that normal VERs to both pattern and flash stimulation can be recorded from area 17, after the destruction of areas 18 and 19, and can be recorded from areas 18 and 19, after the destruction of area 17. However, in both cases the patients had no visual perception and were equally blind.

3.8.0. SUMMARY

As previously shown the most consistently recorded component of the human flash visual evoked potential throughout life is the positive P2 component at around 100-120 msec. The incidence of a recordable earlier positive component, the P1 component, increases with the age of the subject. The amplitude of this earlier positive component also increases with age such that in the elderly it may equal that of the P2 component, to appear the most prominent feature of the flash VER. It is not known why the P1 component cannot be recorded throughout the age range. Two possible explanations present themselves; either that the component develops during middle life or that the P1 component is not absent in the young, but is obscured by a high amplitude P2 component.

The origins of the P1 component also remain unresolved. A functional clue is given by the work in Alzheimer's disease which showed a delay in the latency of the P2 component whilst the P1 component was normal both in latency and in amplitude, as was the pattern reversal response. This led to the proposal that the P1 component and pattern reversal response were of striate origin and the P2 component of extrastriate origin.

None of the topographic studies have addressed themselves to the problem of locating the P1 component of the human flash VER using white unstructured light, although one study located it maximally over the Pz electrode using red light. Other studies have commented on the location of the complete flash VER as being from all or parts of areas 17, 18 and 19.

CHAPTER 4.

THE EFFECT OF RECORDING A FLASH VER THROUGH A CLOSED EYELID.

4.1.0. INTRODUCTION

It is well recognized that the effect of eye closure upon the electroencephalogram (EEG) is to increase alpha activity (Adrian & Matthews 1934). Alpha activity is ongoing brain activity with a frequency of between 8 and 13 cycles per second. The International Federation for Electroencephalography and Clinical Neurophysiology's definition of alpha rhythms is that they are "present most markedly when eyes are closed and attenuated during attention especially visual" (Storm van Leeuwen 1966). Reports as to the effect of eye closure upon the flash visually evoked response (VER) are less numerous. An increase in the amplitude of the early response of the flash VER has been reported (Halliday 1982). Poole and Weaving (1987) showed that with eye closure the P2 component of the flash VER had an increased latency of around 5-10 msec whilst the increase in the latencies of the earlier components was smaller.

The effect of eye closure upon the flash VER is of clinical importance. Recordings of the flash VER may be required from patients who are unable to open their eyes, e.g. from babies, patients with major eye injuries, in cases of drowsiness or indeed where responses are required during sleep.

The reported increase in the latency of the major positive component (P2 occuring at

about 100-120 msec) with a smaller increase in the earlier positive component (P1 occuring at around 60-70 msec) reveals another difference between the P2 and P1 components of the flash VER. The effect on the VER from recording through a closed eyelid could result from the closed eyelid causing a reduction in the intensity of the stimulus; the closed eyelid acting as a red filter; or diffusing the light to act as a Ganzfeld form of stimulation. Alternatively eye closure could cause an increase in the background alpha activity, which may in turn affect the averaged VER record by changing the signal/noise ratio. Since eye closure usually increases the amplitude of the alpha rhythm and since alpha rhythm may indicate lower levels of attention, a further possibility is that the effects on the components of the VER may be related to inattentiveness.

This study investigated the factors above to ascertain which, if any, mimic the effect of eye closure.

4.2.0. METHODS

4.2.1. The Effect of Recording a Flash VER through the Closed Eyelid.

Flash VERs were recorded through a closed eyelid to investigate the effect of eye closure on the P1, N2 and P2 components. Since the P1 component is more readily identifiable as the age of the subject increases (Wright et al 1985) subjects of two different age groups were studied.

The older age group consisted of 10 subjects with a mean age of 52.2 years (range 41-63 yrs). All these subjects were healthy volunteers with no ophthalmolgical or

neurological disorders. Flash VERs were recorded monocularly, from the right and left eyes, in both the eye open and eye closed state. The non-stimulated eye was occluded. In a study of 5 normal subjects it was shown that there was no significant difference between the responses recorded from the stimulated eye, with the occluded eye open or with it closed beneath the occluder. It was not, therefore, necessary to control for the state of the occluded eye. Standard silver - silver chloride electrodes were placed on the scalp at O1 and O2 and referred to Fz. The resistance of the skin electrode interface was reduced to below 5 kohm. Stimulation was provided by a Grass PS22 photostimulator, fitted with a diffusing screen, flashing at 1.1Hz at intensity 2, which is equivalent to 68 cd/m^2 per sec. The photostimulator was placed 33 cms in front of the subject. The high and low pass filters were set at 0.5 and 30 Hz respectively and an average of 50 repetitions was recorded on a Nicolet Pathfinder II. Three recordings were made for each eye, for each stimulus condition. The above recording conditions were identical to those used for a routine clinical VER.

The younger age group consisted of 10 subjects, all healthy volunteers with a mean age of 22.1 years (range 16-28 yrs). Flash VERs were recorded as above.

4.2.2. The Effect of Reduced Intensity of Stimulation on the Latency of the Flash VER.

Flash VERs were recorded with the stimulated right eye closed and then with the right eye open. Four steps of neutral density filter were placed in front of the photostimulator to assess the effect of a reduction in stimulus intensity. The filter steps were from 0.00, a baseline measurement, to 3.00 log units in 1.00 log unit steps. The recording parameters were as described above. The non-stimulated eye was occluded.

4.2.3. The Effect of Mental Activity on the Latency of the Flash VER.

The effect of performing mental tasks whilst recording flash VERs was investigated by recording monocular flash VERs from the right eye with the subjects either in a relaxed state or counting backwards aloud, subtracting serial 7's from a previously given three figure number. These conditions were imposed for both eye open and eye closed runs, with the non-stimulated eye occluded. The recording parameters were as for 4.2.1.

4.2.4. The Light Diffusing Effect of the Eyelid on the Latency of the Flash VER.

Baseline flash VERs were recorded from both the open and closed right eye to white light, the left eye being occluded. The subject then wore a pair of wide angled goggles, fitted with diffusing opal lenses with side flaps in order to produce a Ganzfeld effect, and VERs were recorded from the open right eye, stimulated with either red or white light. The recording parameters were as described in 4.2.1 with the left eye occluded.

4.2.5. The Effect of Different Stimulus Wavelengths on the Latency of the Components of the Flash VER.

VERs were recorded from the open right eye, stimulated by red or green luminance-matched light, whilst the left eye was occluded. To luminance match the red and green light two Medelec OS5 photostimulators were placed side by side flashing alternately at 15 Hz and viewed through a diffusing screen. The position of one photostimulator was set and the distance of the other one from the diffusing screen was

adjusted until minimum flicker was achieved. A red Rosco No. 26 filter was placed in front of one photostimulator and a green Rosco No. 86 filter was placed in front of the other. The photostimulators were viewed flashing at 15 Hz and neutral density filter was placed in front of the green filter until minimum flicker was achieved. Four different observers performed the task and the same result was achieved by them all.

The recording parameters were as described as in 4.2.1 except in this experiment a Medelec OS5 photostimulator was used instead of the Grass PS22 photostimulator. The change in photostimulator was necessary because it was not possible to trigger the Grass PS22 photostimulator at 15 Hz.

4.3.0. RESULTS

4.3.1. The Effect of Recording a Flash VER through a Closed Eyelid.

The results below are for the right hemisphere as there was no significant difference between hemispheres.

The group averaged latency and amplitude values for the older age group are given in Table 4.1 and the group averaged traces are shown in Figure 4.1.

The group averaged latency and amplitude values for the younger age group are given in Table 4.2 and the group averaged traces are shown in Figure 4.2.

Table 4.1:- The group averaged data for both the eye open and eye closed state for the older age group. The figure in parenthesis represent the value of 1 SD.

Latency(msec)		Eye Open	Eye Closed	p value
	P1	73.69 (5.24)	69.53 (8.60)	NS
RE	N2	87.23 (11.84)	89.20 (5.99)	NS
	P2	120.83 (8.49)	133.73 (16.29)	$p < 0.005$
	P1	69.55 (5.87)	72.10 (5.01)	NS
LE	N2	85.90 (9.29)	87.48 (8.47)	NS
	P2	120.56 (10.57)	132.53 (18.71)	$p < 0.01$

Amplitude(μV)		Eye Open	Eye Closed	p value
	N1-P1	4.55 (2.97)	3.10 (1.73)	NS
RE	N2-P2	9.48 (5.03)	8.65 (4.22)	NS
	N1-P1	3.57 (2.91)	3.45 (1.72)	NS
LE	N2-P2	11.40 (5.59)	8.83 (3.94)	NS

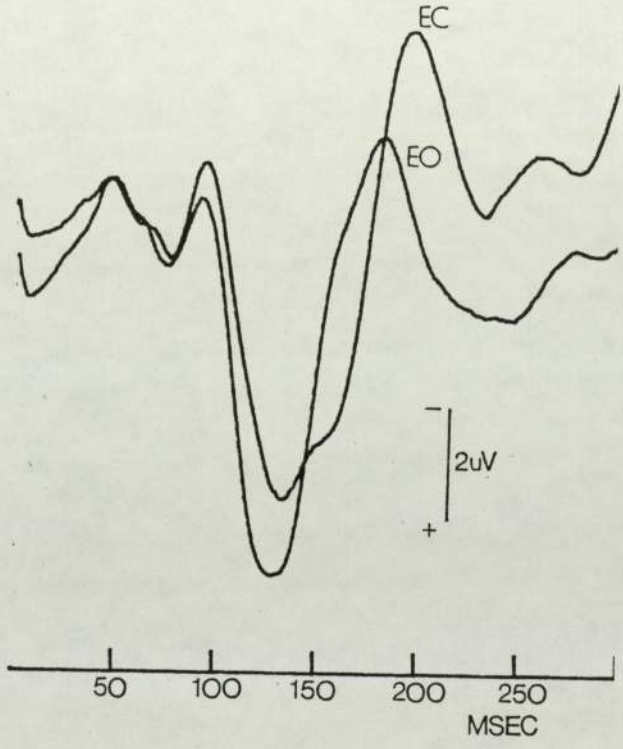


Figure 4.1:- The group averaged flash VER data of the older age group recorded from the open eye (EO) and from the closed eye (EC). The mean P2 latency recorded from the open eye was 121 msec and 134 msec from the closed eye.

Table 4.2:- The group averaged data for both the eye open and eye closed state for the younger age group. The figure in parenthesis represent the value of 1 SD.

Latency(msec)	Eye Open	Eye Closed	p value
RE N2	72.26 (13.22)	84.70 (11.46)	p<0.02
P2	115.50 (8.69)	129.73 (10.34)	p<0.001
LE N2	72.37 (14.2)	78.29 (15.59)	NS
P2	116.63 (6.98)	127.13 (10.49)	p<0.001

Amplitude(μV)	Eye Open	Eye Closed	p value
RE N2-P2	10.17 (5.09)	10.09 (5.09)	NS
LE N2-P2	12.00 (5.09)	9.46 (5.13)	NS

There was a significant increase in the latency of the P2 component when the response was recorded through a closed eyelid in both age groups. The mean increase in the older age group was 12.47 msec (±10.8) and in the younger age group 12.4 msec (±7.14). These increases were significant, using a paired t-test, at the $p<0.01$ level. There was no significant increase in the latency of the P1 component in the older group. It should be noted that whereas in all 10 older subjects a readily identifiable P2 component was recordable from each eye, only 5 subjects showed a recordable P1. The amplitude of the P1 and P2 components recorded through a closed eyelid was not

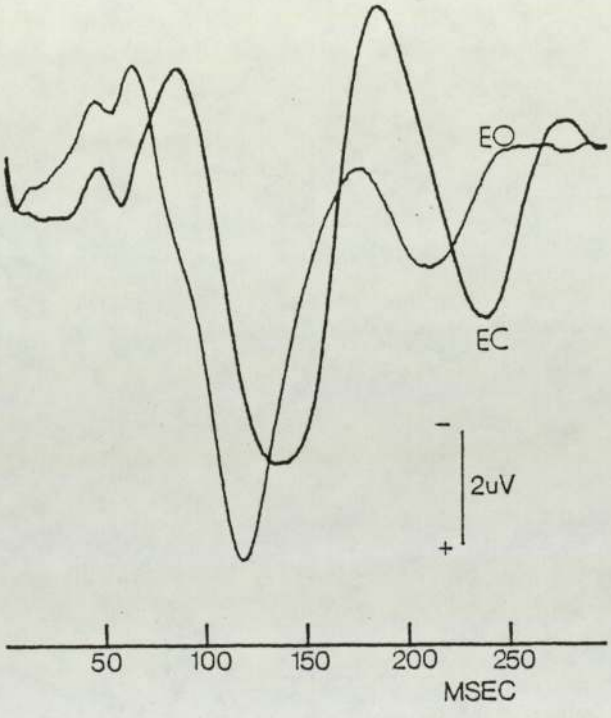


Figure 4.2:- The group averaged data of the younger age group recorded from the open eye (EO) and from the closed eye (EC). The mean P2 latency recorded from the open eye was 116 msec and 130 msec from the closed eye.

significantly different from those recorded from the open eye. The amplitude of the response being measured with respect to the preceding peak.

As previously stated all the results presented below are for the right hemisphere, as there was no significant difference between the hemispheres for the same test conditions, save for one condition in the colour study which will be noted later. The statistical test applied throughout was the paired t-test.

4.3.2. The Effect of Reduced Stimulus Intensity on the Latency of the Flash VER.

As previously stated, the P2 latency recorded when the eye was closed (130 msec ± 7.22) was significantly increased at the $p<0.001$ level compared to the baseline eye open latency (111 msec ± 10.03), with no neutral density filter placed in front of the photostimulator, and there was no significant difference in amplitude of the N2-P2 component recorded. The placing of neutral density filters in front of the photostimulator did not significantly alter the P2 latency (Figure 4.3).

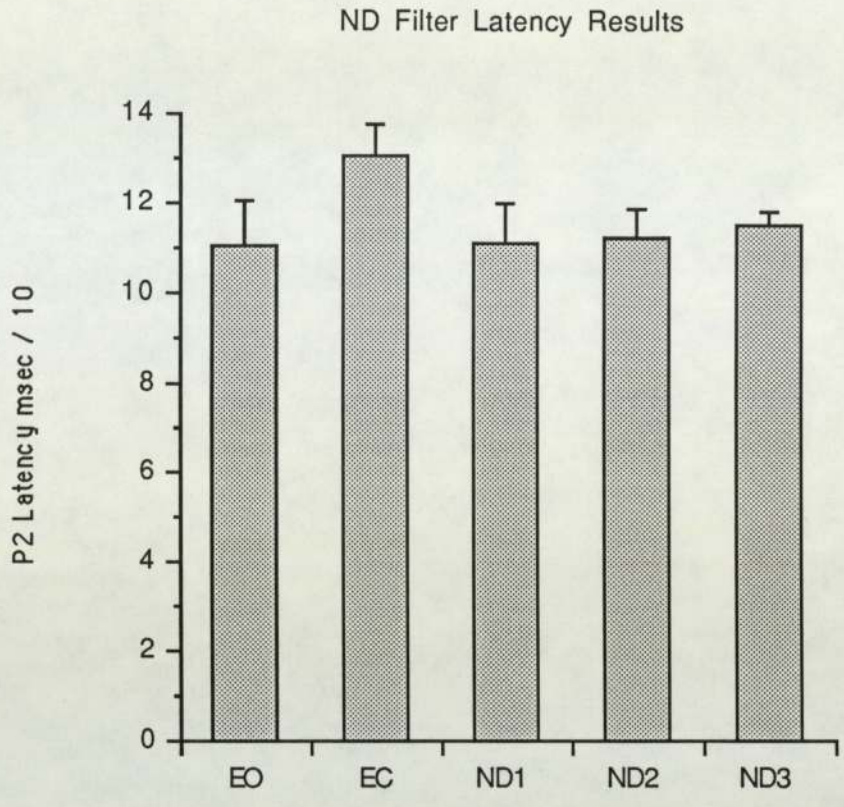


Figure 4.3:- Group averaged P2 latency results for eye open (EO), eye closed (EC) and neutral density filters (ND). Error bars represent '+' 1 S.D.

In addition there was no significant difference in the amplitude of the response recorded until the neutral density filter had reached 3 log units, at which point the reduction in amplitude reached statistical significance at the $p<0.005$ level (Figure 4.4).

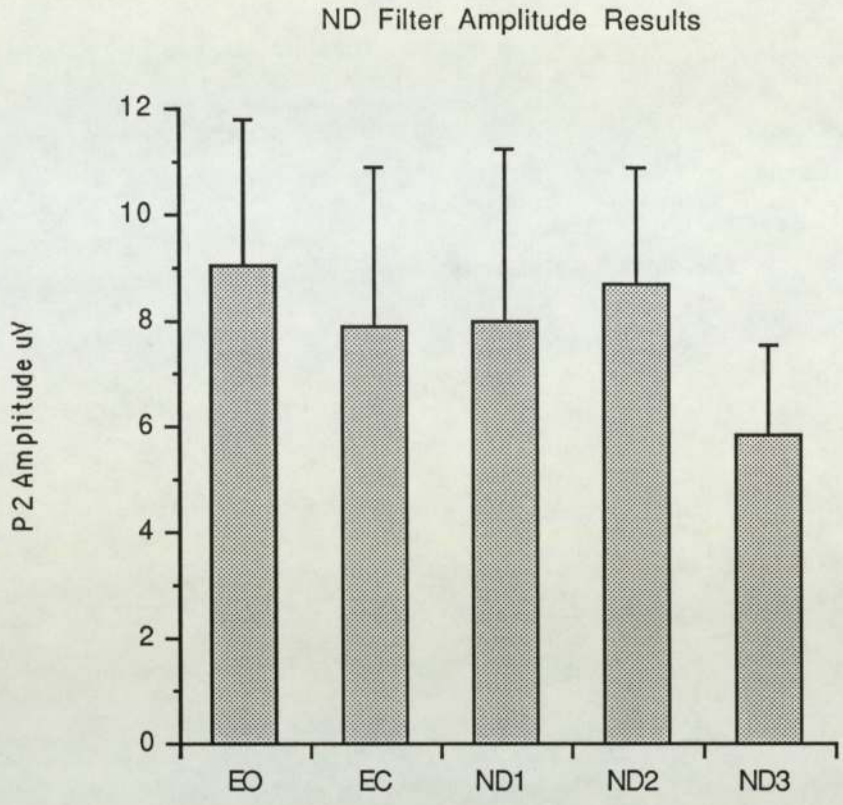


Figure 4.4:- Group averaged P2 amplitude results for eye open (EO), eye closed (EC) and neutral density filters (ND). Error bars represent '+' 1 S.D.

The group averaged traces presented in Figure 4.5 show the reduction in amplitude resulting from the use of a 3 log unit neutral density filter, with no concurrent increase in latency.

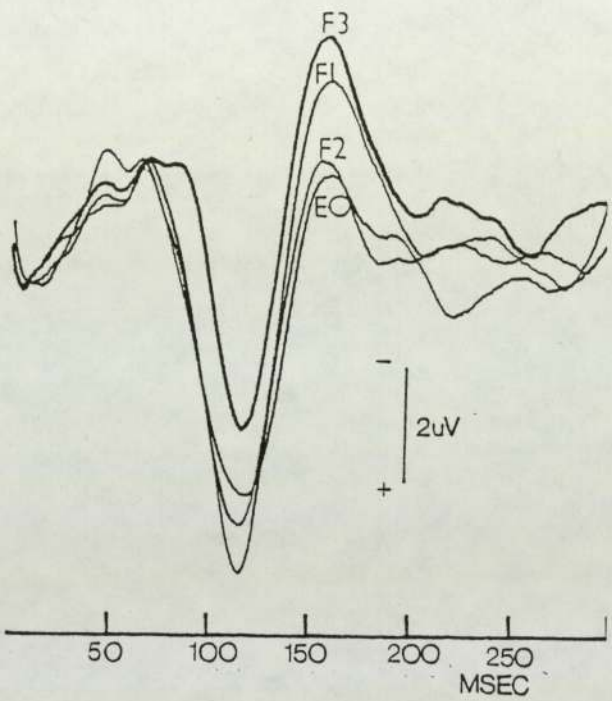


Figure 4.5:- The group averaged data of the filter study showing a significant reduction in amplitude of the P2 component with the use of a 3 log unit neutral density filter (F3) compared to no filter used (EO), a 1 log unit filter (F1) or a 2 log unit filter (F2).

4.3.3. The Effect of Attention on the Latency of the Components of the Flash VER.

The mean eye open P2 latency was 117 msec (± 4.18) compared to the mean eye closed P2 latency of 133 msec (± 6.61) and this was significantly different at the $p<0.001$ level. The performance of a mental task had no significant effect on the P2 latency recorded in either the eye open or the eye closed states. The P2 latency from the closed eye, whilst performing a mental task, was still significantly longer than that recorded from the open eye ($p<0.001$) (Figure 4.6 & 4.7).

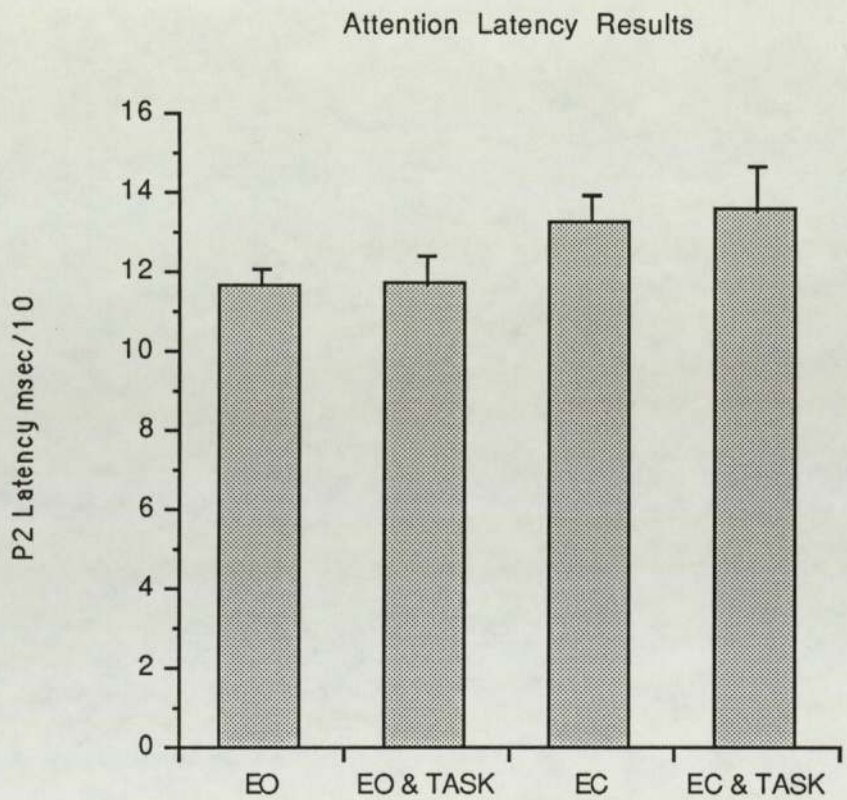


Figure 4.6:- Group averaged P2 latency results for eye open (EO) and eye closed (EC) situations with and without a mental task. Error bars represent '+' 1S.D.

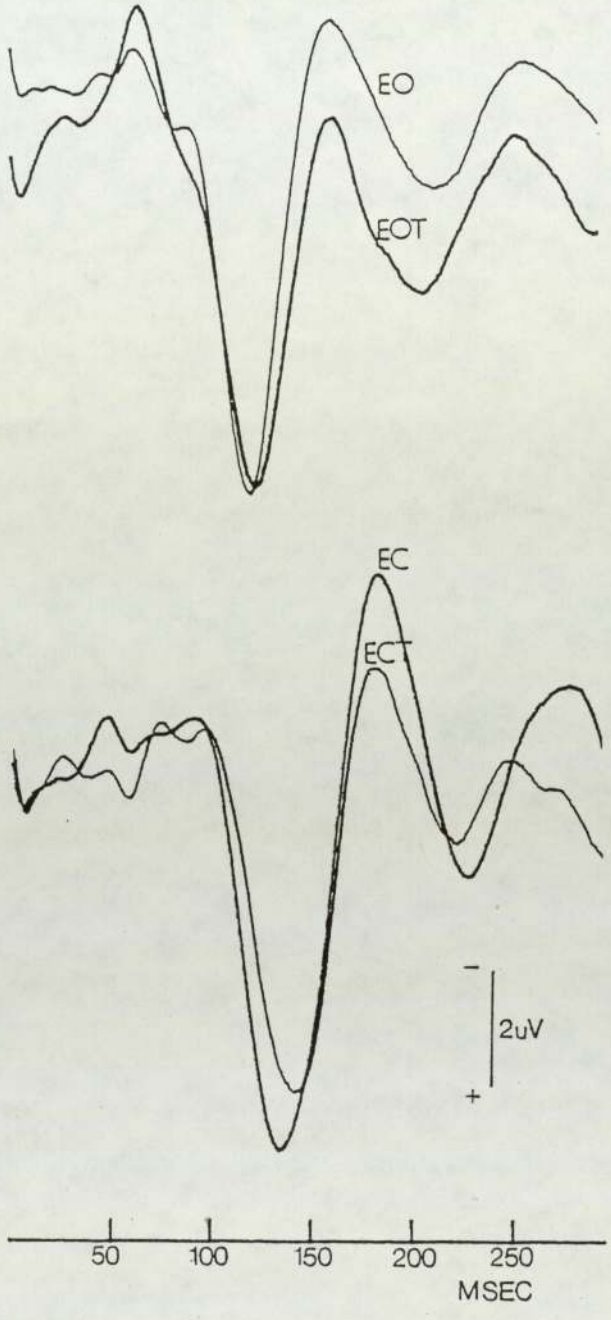


Figure 4.7:- The group averaged data of the attention study showing the P2 component has a longer latency when recorded through a closed lid (EC) compared to an open eye (EO) and that the performance of a mental task (T) had no significant effect on the latency of the component recorded.

4.3.4. The Light Diffusing Effect of the Eyelid on the Latency of the Flash VER.

The group averaged results showed a significant increase in the latency of the P2 component with the eye closed (133 msec ±12.97) compared to the baseline eye open recording (120 msec ±11.34) at the $p<0.001$ level (Figure 4.8 & 4.9). The latency of the P2 component to white light was not significantly altered by the use of a Ganzfeld form of stimulation (122 msec ±10.80). The latency of the P2 component recorded using red light with a Ganzfeld form of stimulation (135 msec ±8.20) was not significantly different from the latency of the P2 component recorded from the closed eye (133 msec). It was, therefore, significantly longer than the P2 latency recorded from the open eye with white light (120 msec) at the $p<0.001$ level.

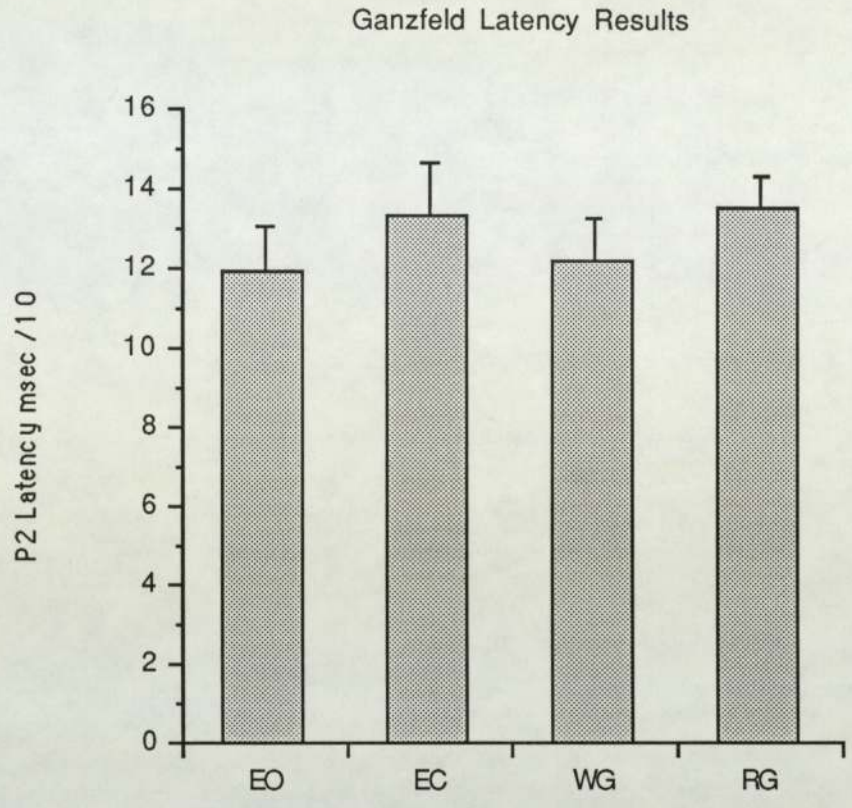


Figure 4.8:- Group averaged P2 latency results for eye open (EO), eye closed (EC), white Ganzfeld (WG) and red Ganzfeld (RG). Error bars represent '+' 1 S.D.

4.3.5. The Effect of Different Stimulus Wavelengths on the Latency of the Components of the Flash VER.

As for all the previous experiments there was a significant increase in the latency of the P2 component of the flash VER recorded from the closed eye (128 msec ±11.07) compared to the eye open situation (116 msec ±6.72), but on this occasion the effect was only apparent for the right hemisphere ($p<0.02$), the results for the left hemisphere did not reach significance ($p<0.07$) (Figure 4.10 & 4.11). There was no significant

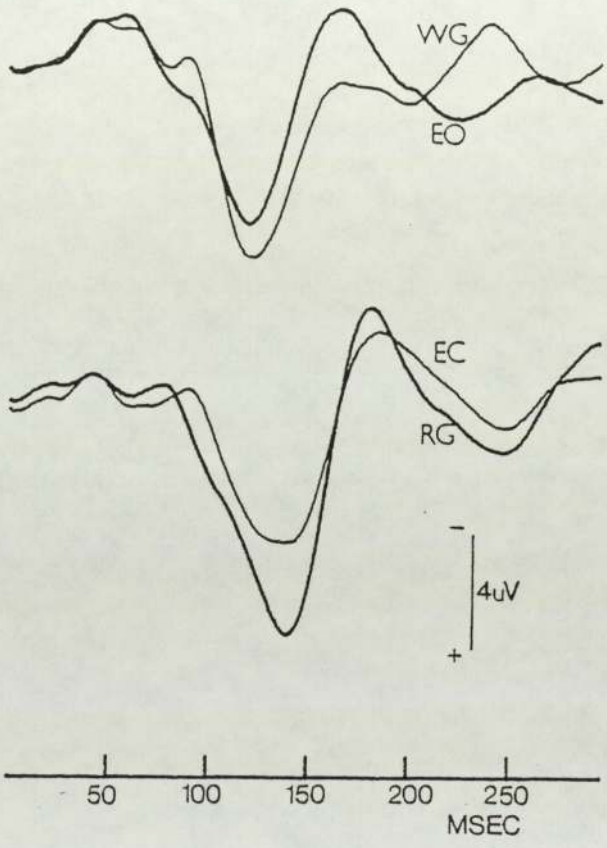


Figure 4.9:- The group averaged data of the Ganzfeld study showing that the latency of the P2 component is longer when recorded through a closed eyelid (EC) or when using red light and a Ganzfeld form of stimulation (RG) compared to recording from an open eye (EO) or using white light and a Ganzfeld form of stimulation (WG).

difference in the latency of the P2 component recorded from the open eye to either white or green light stimulation. The latency of the P2 component recorded from the open eye to red light was, however, significantly longer (131 msec ± 16.99) than that recorded with white (116 msec) or green light stimulation (115 msec ±8.71) (at the $p<0.006$ level) although it was similar to the P2 latency recorded from the closed eye to white light (128 msec).

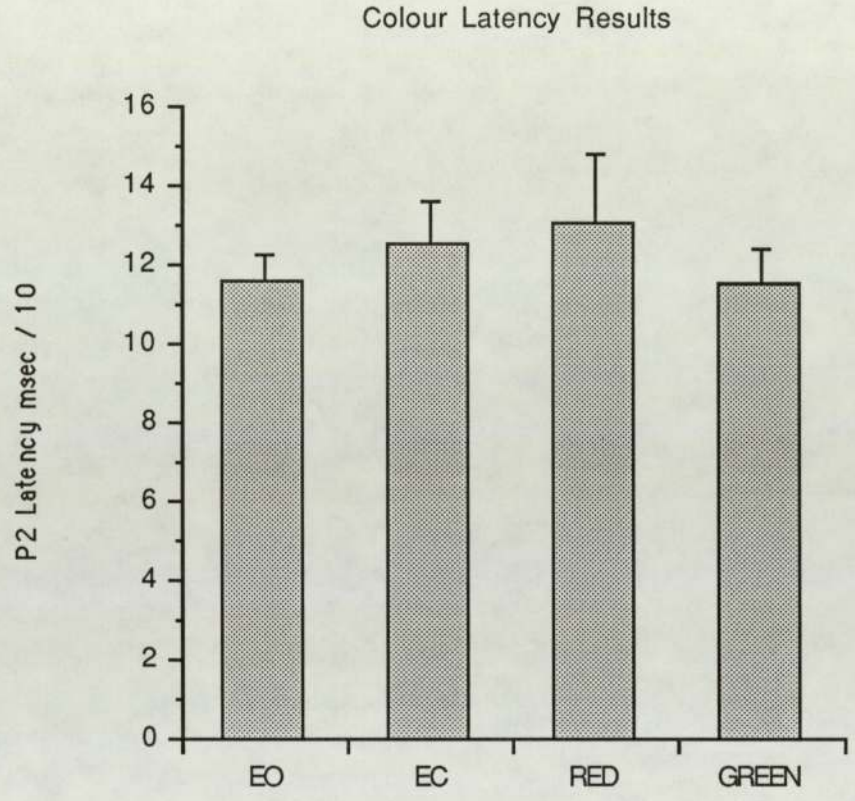


Figure 4.10:- Group averaged P2 latency results for eye open (EO) and eye closed (EC) to white light and for eye open to red and green light. Error bars represent '+' 1 S.D.

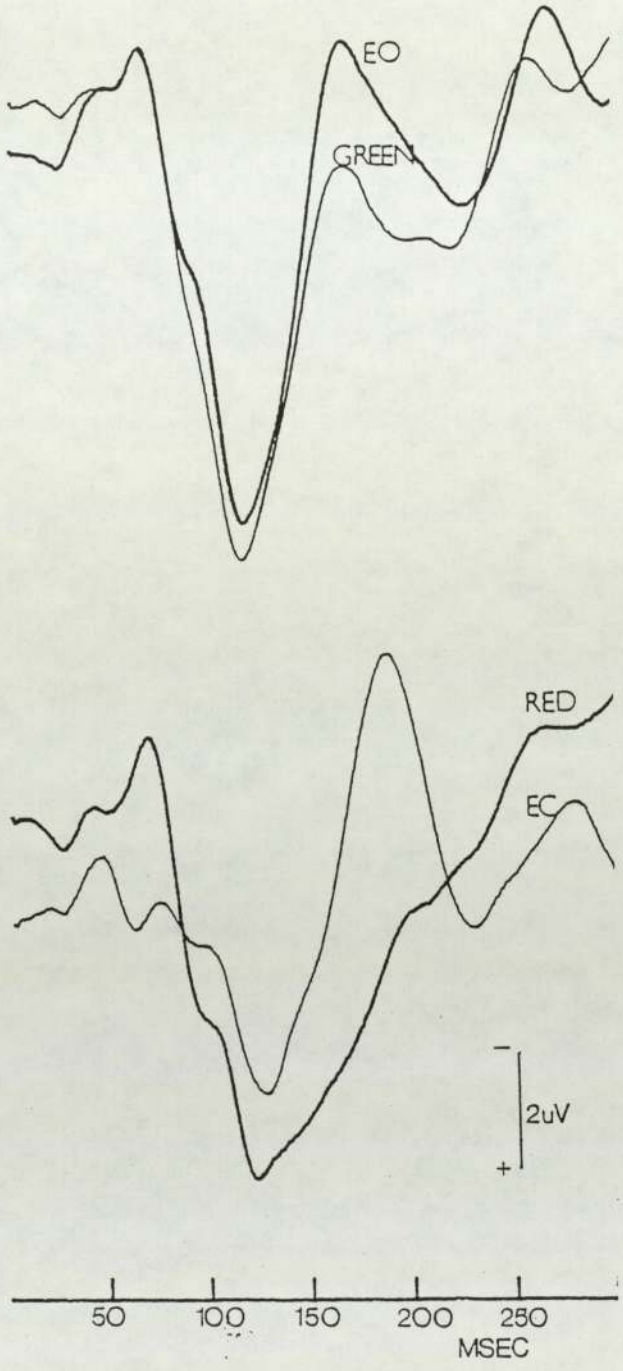


Figure 4.11:- The group averaged data of the colour study showing no significant difference in the latency of the P2 component between white light (EO) and green light stimulation and similarly no significant difference between eye closed (EC) and red light stimulation. However, the latency of the P2 component recorded through a closed eyelid or to red light is significantly longer than the two traces above.

4.4.0. DISCUSSION

The results showed that when a closed eye was stimulated by a flashing white light, the P2 component of the VER recorded had a significantly longer latency compared to that recorded when the eye was open, confirming the findings of Poole & Weaving (1987). There was no such effect on the latency of the P1 component. There was no significant effect upon the amplitude of responses recorded for either the P1 or P2 components. The latencies and amplitudes recorded for the eye open condition were in agreement with previously published normative results (Wright et al 1985). As a practical clinical point these findings indicate that eye closure has no significant effect upon the amplitude of the response within the range of intensities used for stroboscopic stimulation.

There was no significant increase in the latency of the P2 component when neutral density filters were placed in front of the photostimulator. This finding is in agreement with Thorpe Davis et al (1987). These results suggest therefore, that the increase in the P2 latency when the eye is closed is not due to the reduction in the luminance of the stimulus produced by the closed eyelid. Whereas a significant reduction in the amplitude of the response compared to the eye open value, resulted from the use of the 3 log unit neutral density filter placed in front of the photostimulator, there was no significant difference between the eye open and eye closed amplitudes at normal photostimulator intensity. In order to control for discrepancies in intensity four subjects were studied at an additional intensity of 8 and one subject at intensity 16. The increase in latency on eye closure was approximately the same at all intensities. This would again suggest that the effect of eye closure on the P2 component is not one of luminance variation.

There are conflicting views as to the effect of a mental task such as mental arithmetic on the amount of alpha activity in the underlying EEG. These vary from attenuation of alpha activity in all or almost all subjects (Lorens & Darrow 1962, Walter 1959) to attenuation only in certain people (Mundy-Castle 1957) to having no effect on the underlying alpha activity (Mulholland 1969, Creutzfeldt et al 1969) or even increasing it (Kreitman & Shaw 1965). If the increase in latency of the P2 component, when the eye was closed, was due to an increase in alpha activity in the underlying EEG, then recording the flash VER through a closed eyelid while the subject performed mental arithmetic tasks could alter the background alpha activity and reduce the effect of eye closure on the P2 latency. The performance of such a mental task had no effect on the P2 latency when the flash VER was recorded with the eye open or closed.

This would suggest that the increase in P2 latency was unrelated to the amount of background alpha activity, or that the mental arithmetic task did not cause attenuation of the underlying alpha activity. Alternatively there maybe more than one generator of alpha rhythm in the brain and perhaps different types of the alpha rhythm are affected differently by different attention demanding tasks. It would appear that if the P2 latency was being affected by alpha activity it was not the type of alpha activity which is attenuated by mental arithmetic.

The results from the Ganzfeld study suggest that the increase in the P2 latency was not related to the eyelid diffusing the light, and thus providing a Ganzfeld effect, but could be related to the closed eyelid acting as a red filter.

The Ganzfeld study had suggested and the colour study showed that the use of a red filter in front of the photostimulator did indeed produce a P2 latency that was significantly greater than in the eye open response, but was similar to the eye closed response. This would suggest that the increase in P2 latency is due to the eyelid acting as a red filter.

This finding is supported by the work of Crawford & Marc (1976) who measured the transmission spectra of the monkey eyelid in vivo and found that 15 - 25% of the transmission was of the longer wavelengths. Moseley & Fielder (1987) and Moseley et al (1988) have attempted to replicate this work in humans and achieved similar results. Previous studies using red as the stimulus wavelength have either shown no effect upon the P2 latency of the response recorded (Siegfried 1970, Paulus et al 1984) or that the P2 component to red stimulation was recorded earlier than for blue or green stimulation (White et al 1977). Siegfried's results (1970) were, however, obtained from two subjects and it is known that the flash response varies widely within the normal population (Harding 1982). Paulus et al (1984) used a LED stimulator, with a white surround, to generate different wavelengths of equal brightness. Although they showed no change in the P2 response, they did obtain a more prominent N2 component when stimulating with red light. White et al (1977), using a stroboscope with Wratten filters obtained an earlier P2 response with red stimulation than with the blue or the green. However, they do not state exact subject numbers and most of the data presented is from one subject. Comparison of previous studies is made difficult by the use of different stimulus parameters. A number of studies used Maxwellian view, patterned flash stimuli, varying backgrounds or different reference sites whereas in this study a standardized clinical set up was maintained throughout (Harding 1974).

It should be noted that the P1 latency does not increase significantly when a flash VER is recorded through a closed eyelid in contrast to the P2 component. This would suggest that the generators of the P1 and P2 components are different.

CHAPTER 5

THE TOPOGRAPHY OF THE P1 COMPONENT OF THE FLASH VER.

5.1.0 INTRODUCTION

It was concluded in the previous chapter that the P1 and P2 components of the flash visual evoked response may originate from different anatomical sites. In addition, a review of the literature showed that the morphology of the components of the flash VER vary with the age of the subject. Wright et al (1985) have shown that the incidence of a recordable P1 component increases with the age of the subject and that in the elderly its amplitude may exceed that of the P2 component, such that it appears to be the most prominent feature of the flash VER. Although studies have examined the effect of age on the latency and morphology of components of the flash VER (Harding 1982, Cosi et al 1982, Wright et al 1985) there have been few studies which looked at the topography of the P1 component and none which studied topographical variations with respect to age. Nakamura & Biersdorf (1971) looked at the early components of the flash VER, (i.e. those recorded before 100 msec), using red light, and found that the P1 component was maximal over the Pz electrode. No other studies have been found that specify a topographical location for the P1 component.

A study was therefore devised to use the 20 channel Biologic Brain Mapping System to

look at the topography of the P1 component of the flash VER, especially with respect to its variation with age.

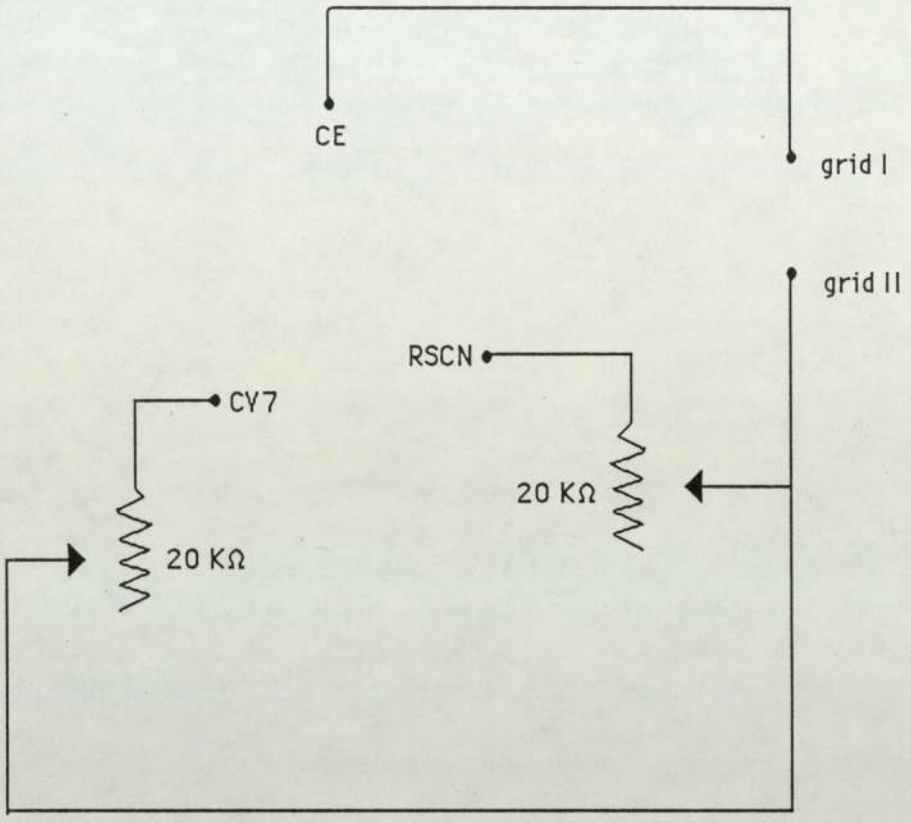
5.2.0 METHODS.

Flash VERs were recorded from thirty subjects ranging in age from 21-84 years. All were healthy with no ophthalmological or neurological disorders. The subjects recruited fell into one of three age groups 20-40 years (the young age group), 40-60 years (the middle age group) and 60+ years (the old age group). The young age group consisted of four males and six females, with a mean age of 26 years (range 21-33 years). The middle age group consisted of four males and six females, with a mean age of 49.4 years (range 41-59 years). The old age group consisted of five males and five females, with a mean age of 72.5 years (range 64-84 years).

Twenty standard silver-silver chloride electrodes were placed on the scalp according to the international10-20 system (Jasper 1958). The Biologic Brain Mapping system is a 20 channel averager and in these studies an electrode was placed at Oz but not at Fpz, therefore the data for Fpz was interpolated. The electrodes were attached with tape and the resistance of the skin electrode interface was reduced below 5 kΩ. The standard 10-20 electrode positions were chosen in preference to a grid system, or a customised montage, as previous work had suggested that the flash response was widespread and not confined to area 17 (Orwin et al 1986, Nakamura & Biersdorf 1971, Wright et al1987). Thus the placing of the electrodes according to the 10-20 system was a good starting point from which a customised montage could be devised if the responses recorded so indicated.

All the electrodes were referred to a balanced non-cephalic reference (BNCR) designed by Stephenson & Gibbs (1951) (Figure 5.1). One electrode was placed on the right sterno-clavicular joint and the other was placed on the spinous process of the seventh cervical vertebra, the vertebra prominens. The resistance the skin electrode interface of the two reference electrodes was reduced equally below 5 kΩ. It was found that if the resistance of one of the pair of electrodes deviated from a common resistance below 5 kΩ by more than 2-3 kΩ one invariably had problems with noise during the recording. The leads of the reference electrodes were joined via two variable 20 kΩ potentiometers which were adjusted to balance out the electrocardiogram (ECG). The elimination of the ECG is achieved by recording EEG referred to the BNCR and adjusting the potentiometers one at a time to eliminate the characteristic Q, R, S waves of the ECG (Figure 5.2) until there is no trace of the ECG in the EEG trace. It was easier to achieve the elimination of ECG if the subject was supine rather than sitting.

The BNCR was the reference of choice as the aim of the study was to map the topography of the response from electrodes placed evenly over the whole scalp. A reference electrode placed on the scalp therefore could not be inactive and the choice of point of reference would have an effect on the map recorded. It is also important with the choice of reference site that the responses recorded are reproducible and that changes do not occur either within the time of a single sweep, thus affecting relative amplitude of succesive components, or over the time of an experimental recording session. The BNCR was found to be a stable reference over time as traces recorded at the beginning of a one hour session were very similar to the traces recorded at the end of the session (Figure 5.3). Equally the probability of a visual stimulus inducing a vagal or other responses was extremely unlikely.



CE = cerebral electrode
CY7 = cervical vertebra
RSCN = right sternoclavicular notch

Figure 5.1:- Circuit diagram of the balanced non-cephalic reference (modified from Stephenson & Gibbs 1951).

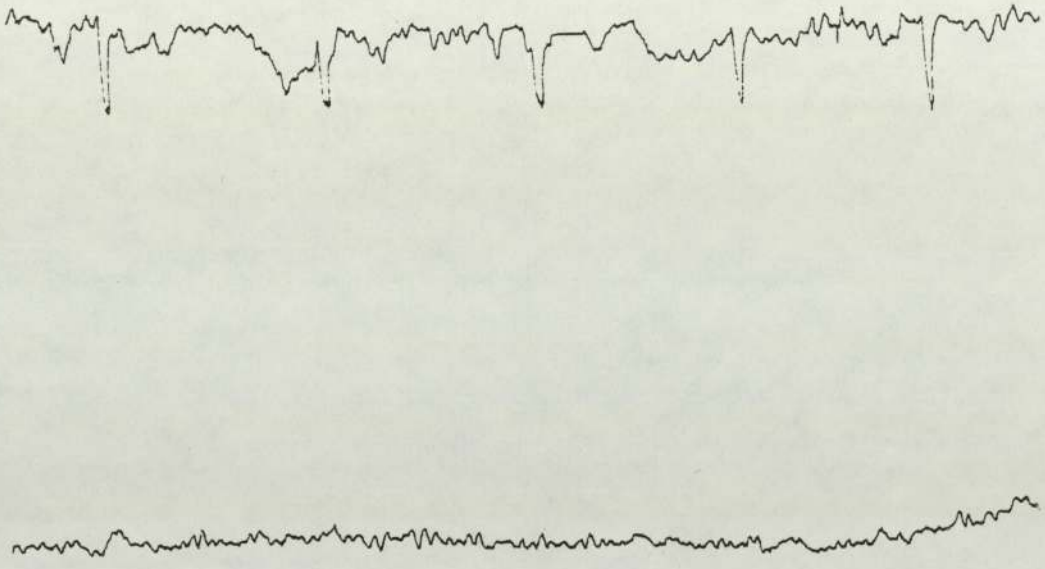


Figure 5.2:- The top trace shows EEG recorded from Fz referred to the BNCR before elimination of the ECG. The filters were set at 0.3 and 60 Hz and the gain was 1. The lower trace shows the EEG recorded from Fz, in the same subject, referred to the BNCR after the elimination of the ECG. The recording parameters and gain were as for above.

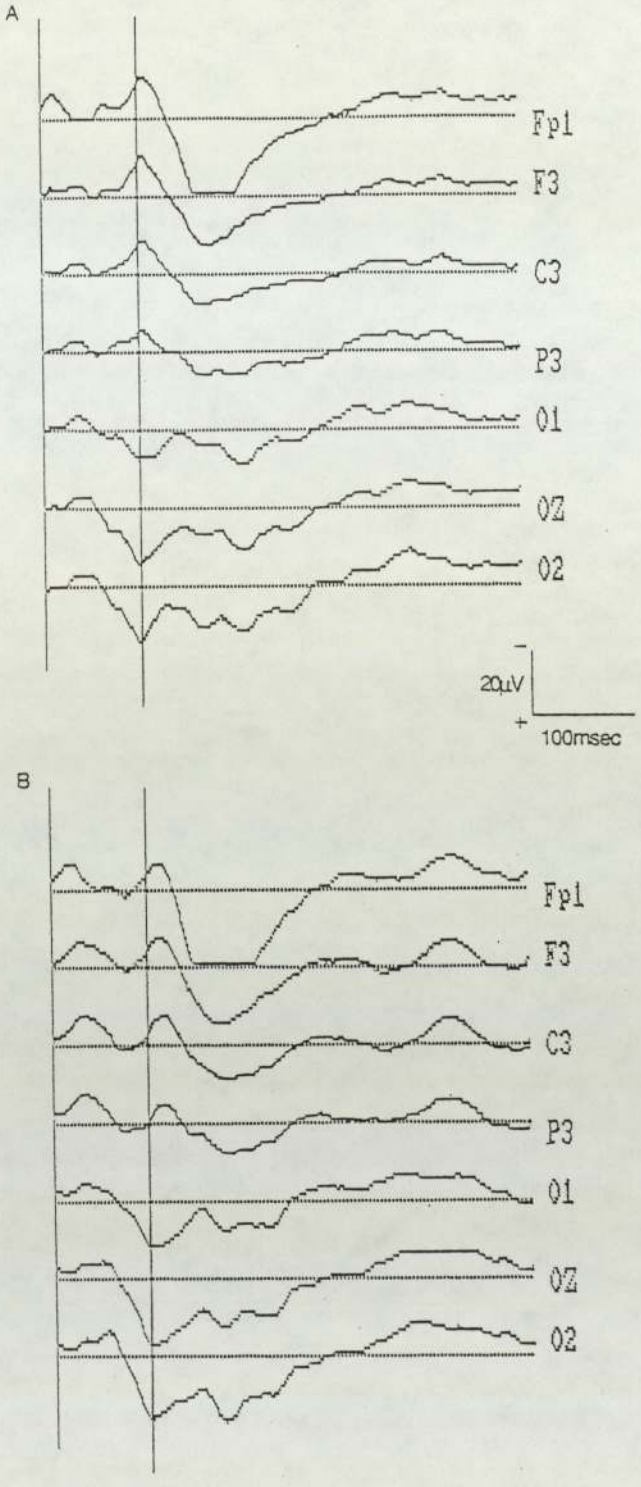


Figure 5.3:- This figure demonstrates the reproducability of responses using a balanced non-cephalic reference. The major positive component in both traces is at 104 msec.

The stimulation used to elicit the responses was a Medelec OS5 photostimulator flashing at intensity 2, at a rate of 1.1 Hz. The light output from the Medelec photostimulator is equivalent to that of the Grass PS22 photostimualtor (Harding et al 1987) and therefore the stimulus intensity was equivalent to 68 cd/m^2. The Medelec OS5 photostimulator makes an audible click on discharge and to mask the click of the photostimulator all subjects wore headphones. Initially white noise was employed but the subjects found this uncomfortable after a period of time and occluding headphones were preferred. All subjects were questioned to ensure that the click of the photostimulator was inaudible. A non-stimulus run was performed on a couple of subjects. This involved subjects wearing a pair of light excluding goggles, in addition to the headphones and the photostimulator discharging as normal. The resulting average showed no clear or consistent components either occipitally or centrally (Figures 5.4 & 5.5). The Medlec OS5 was used instead of the Grass PS22 photostimulator for purely practical reasons as the Biologic Brain Mapping system would not trigger the Grass PS22 photostimulator.

The Biologic Brain Mapping system was used to record the responses. The Biologic Brain Mapper is based upon the Zenith microprocessor incorporating a 8088 16-bit processor to give 320K bytes of dynamic RAM. Data was stored on a 10 megabyte Winchester hard disc. Recordings were made from 20 channels with up to eight waveforms being displayed simultaneously. The noise level is 0.6 microvolts RMS. The high and low pass filters were set at 0.3 and 30 Hz respectively, with the roll off of the filters being 12dB/octave. The sample resolution is 2 msec i.e. 256 data points in an anlaysis time of 512 msec. The machine will not record a response until it has completed its own internal calibration. It is also possible to check the calibration externally. This is achieved by putting a 500 Hz pure tone burst into the head box by means of a system

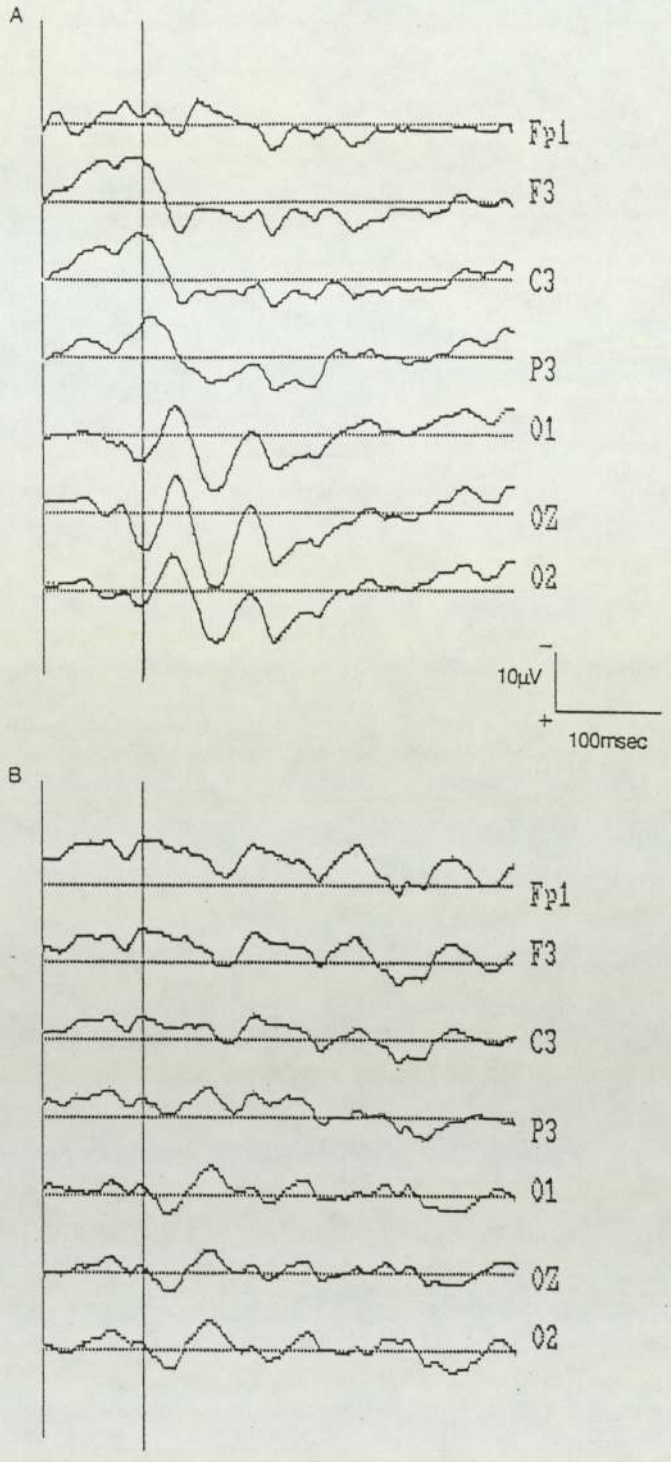


Figure 5.4:- A comparison of a stimulus run (a) with a nonstimulus run (b). A clear positive P2 component is seen in (a) at 110 msec whereas in (b) there are no clear components either occipitally or centrally. Alpha rhythm is clearly present in traces from the non-stimulus run.

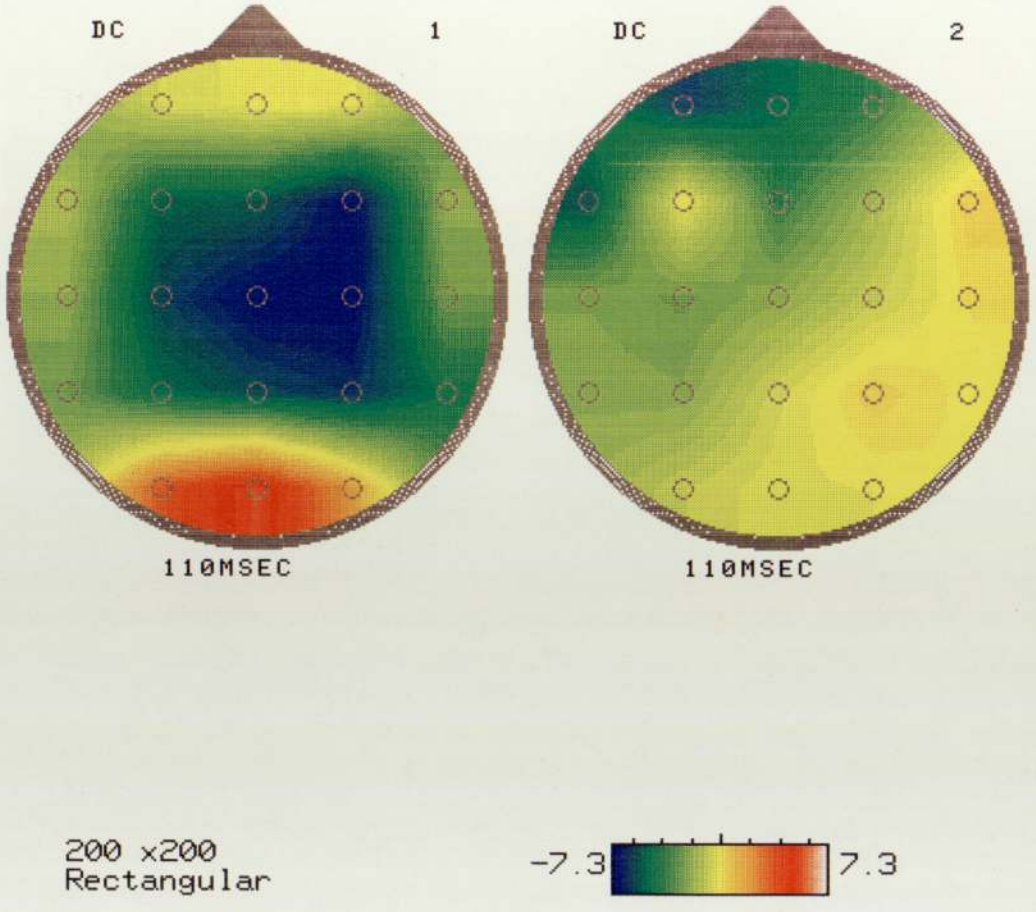


Figure 5.5:- This figure shows the brain maps, at 110msec, of the data shown in figure 5.4. The map on the right being of the non-stimulus run. The lefthand figure shows a clear positive component (P2) occipitally and a negativity centrally and frontally. The map of the non-stimulus run shows no clear components.

loop test box. An average is then recorded, the result of which is a sinusoidal waveform on all channels. If the calibration is correct and all channels are equal then the mapping of the sinusoidal should present a map of identical colour across the head.

The subjects lay on a bed and an average of 64 repetitions was recorded to both binocular eye open and eye closed stimulation. Each of the recordings were repeated.

The Biologic Brain mapping System generates colour maps by means of a four electrode rectangular linear interpolation algorithm. There is no weighting incorporated into the system. There are seven colour scales ranging from an 8 colour scale to a 32 colour scale. Each colour, depending on the gain used, represents a voltage range in μV. Thus if the 32 colour scale is used to represent a voltage range of +5.31 to -5.31 μV each colour will be more specific to a certain voltage than if the voltage range covered is +21 to -21 μV. The maps can then be printed by means of a colour plotter. The quality of the printed plots are not up to thesis standard and thus for ease and clarity of presentation the maps displayed in this thesis have been plotted using a Nicolet Pathfinder II. Voltage readings, at the desired latency, are read from each channel of data recorded on the Biologic Brain Mapping System and transferred to the Pathfinder Nicolet II and a potential map of that data is created. The maps are calculated using a rectangular four electrode linear interpolation algorithm in the same manner as the Biologic Brain Mapping System. The Nicolet Pathfinder also has the facility to plot more than one map on the same piece of paper.

5.3.0. RESULTS

Analysis of the group averaged results showed that there was no difference at comparative electrode sites on each hemisphere and for statistical analysis of the waveforms the recordings from a chain of electrodes down the left parasaggital region of the head Fp1, F3, C3, P3, and O1 were used.

5.3.1. THE TOPOGRAPHY OF THE FLASH VER RECORDED WITH THE EYES OPEN.

5.3.1a THE P2 COMPONENT.

The P2 component was recorded consistently over the occipital region throughout the three age groups (Figures 5.6 & 5.7). The latency of the component was significantly different for all three age groups using a one way analysis of variance test ($F=20.13$; $df=2,48$; $p<0.001$). The mean latency of the component increased with age from 105.87 msec in the young age group to 132.44 msec in the old age group. A frontal negative component at around the same latency as the positive occipital P2 component was recorded with equal consistency, to be termed the N120 component in accordance with its average latency. For the middle and old age group there was no significant difference in latency of the negative component recorded on the frontal channel (F3) and the positive component recorded on the occipital channel (O1) by means of a paired t-test. However, the latency of the frontal negative in the young age group was significantly later ($p<0.01$ by means of a paired t-test) than the latency of the positive

Figure 5.6:- This figure shows the group averaged data, to binocular flash stimulation, and shows a clear P2 component over the occipital region in all three age groups at 106 msec in the young, 120 msec in the middle age group and 132 msec in the old age group. A frontal negative component is found to occur at around the same latency as the positive occipital component in all age groups.

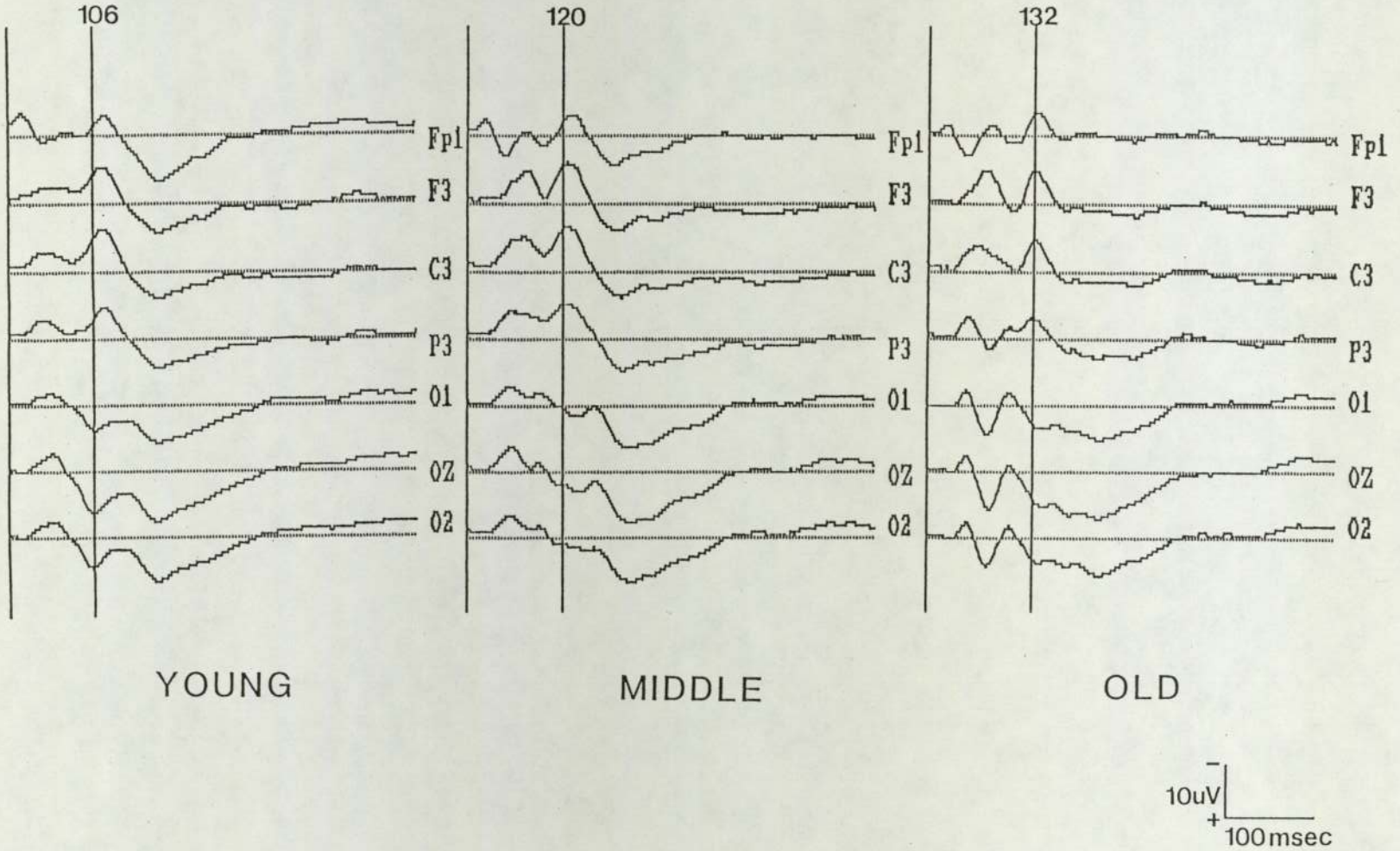
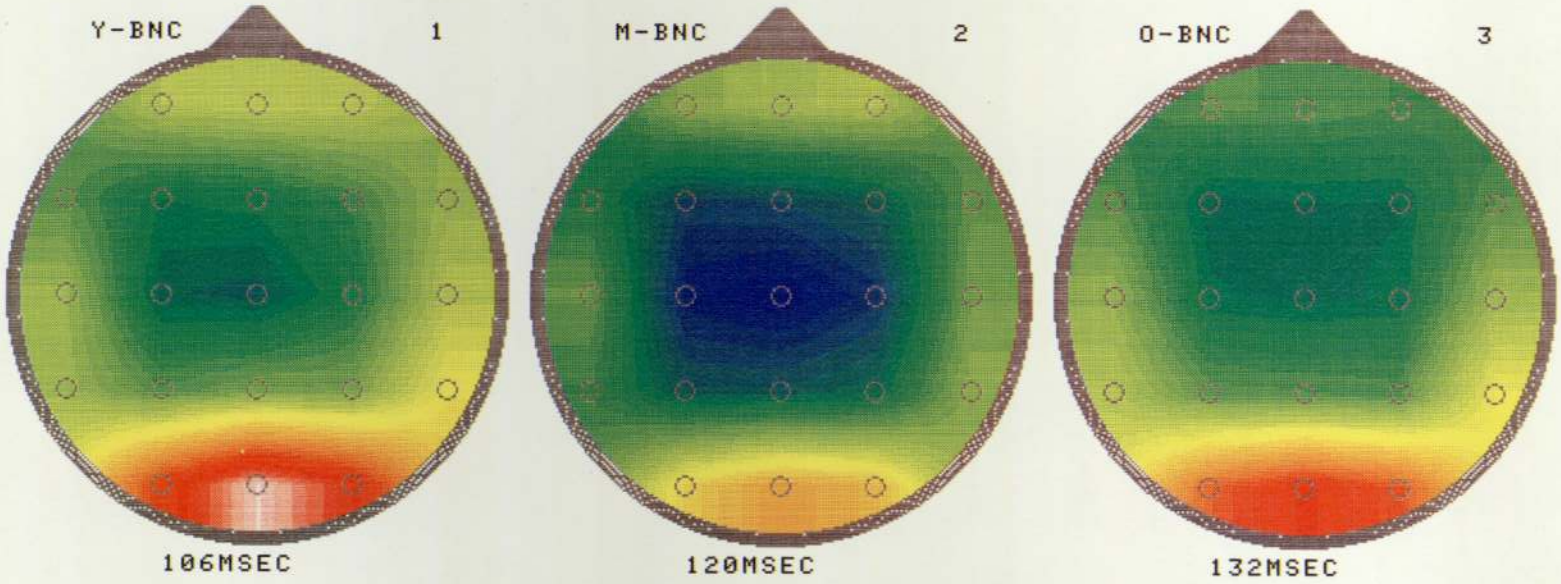
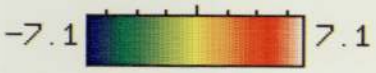

106
120
132
Fp1
F3
C3
P3
01
0Z
02
YOUNG
MIDDLE
OLD
10uV
100msec

Figure 5.7:- This figure shows the brain maps for the group averaged data that was shown in figure 5.6 and illustrates the topography of the P2 component across the age range. All three maps show the positive P2 component over the occipital region with the negative activity over the frontal and central regions.



200 x200
Rectangular



MAP
Nicolet Pathfinder TMAP

component on the occipital channel. The group averaged latency data, of all three groups, for the components recorded at around 100-120 msec are given in Table 5.1.

The amplitude of the frontal N120 or occipital P2 component, measured from the preceding peak, showed no significant difference between groups on all electrodes. The amplitude values are given in Table 5.1.

The identification of components on the traces recorded from the parietal electrodes is not as clear as for the other recording electrodes, as it is around this region of the brain that the two fields from the opposing frontal negative and occipital positive potential meet sometimes producing an apparent polarity inversion of the component. In some individuals the component seen on the trace recorded from the P3 electrode was positive and in others it was negative, accounting for the smaller mean amplitude value for all age groups (Figure 5.8). Another factor contributing to the problem of component identification over the parietal region is that of 'beating'. The component recorded from the central electrodes above is clearly negative and the component recorded from the occipital region below is positive, and thus on the parietal electrodes the identification of the component is not as clear since the negative component becomes superimposed on the positive component resulting in a W-shaped triphasic component.

GROUP	LATENCY FP1	F3	C3	P3	O1	AMPLITUDE FP1	F3	C3	P3	O1
YOUNG	119.07	116.21	117.3	116.74	105.87	-7.99	-6.19	-6.9	-4.77	8.44
±1SE	1.1	1.43	1.38	2.37	3.17	0.8	0.74	0.59	1.29	0.99
MIDDLE	124.77	123.5	123.9	123.75	119.62	-7.37	-7.29	-6.61	-3.42	7.89
±1SE	2.54	1.73	1.77	2.95	2.91	0.79	0.63	0.68	1.47	1.47
OLD	134.38	132.82	134.86	133.5	132.44	-7.62	-8.85	-8.28	-1.94	9.35
±1SE	1.55	1.34	1.04	2.55	2.84	1.07	1.33	1.05	1.96	1.21

Table 5.1:- The group averaged latency and amplitude data for all three groups for the negative and positive components recorded at around 100-120 msec to binocular flash stimulation.

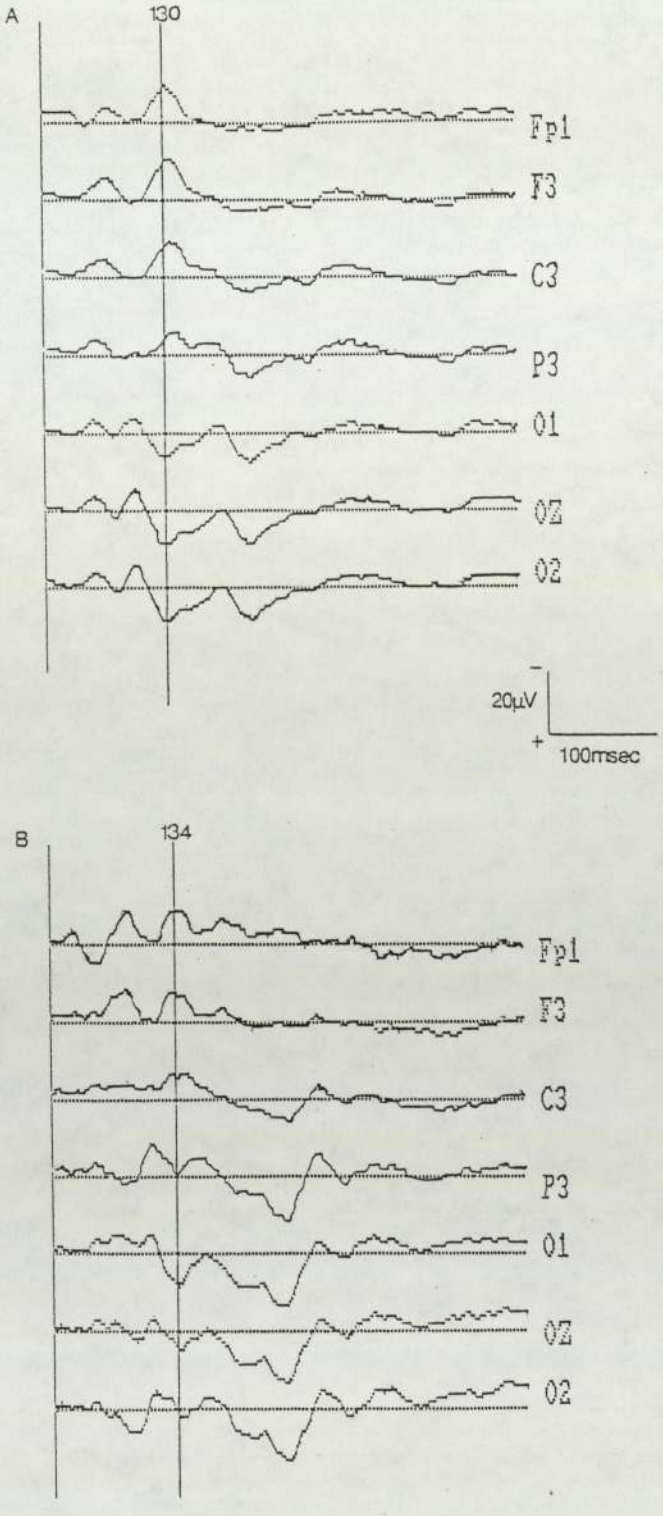


Figure 5.8:- This figure shows the variability of component polarity recorded from the P3 electrode between individuals, whereas the components recorded from other electrodes show a consistency of polarity. The traces are from two individuals in the old age group recorded to the same parameters.

5.3.1b. THE P1 COMPONENT.

The group averaged traces from the study shows that there is no identifiable P1 component in the young and middle age groups whilst in the old age group it was clearly present with a latency of 78.89 msec (Figures 5.9 & 5.10).

At about the same latency a negative component (N75) was recorded on the frontal channels of both the old and middle age groups but not of the young age group. Although the group averaged traces suggests that the middle age group does not demonstrate a P1 component, when the individual traces were examined it became apparent that some of the individuals showed signs of developing a P1 of somewhat reduced amplitude. The fact that 15 of the 20 traces showed a frontal negative, whilst only 9 showed a P1 component, and that in all cases a P1 occured in conjunction with a frontal negative suggests that the frontal negative develops before the P1, rather than the two developing synchrously. In the old age group a P1 component was present on 18 of the traces and a frontal negative on 19 of the traces. There was no comparable positive or negative component for the young age group on any of the twenty traces.

There was no significant difference between the old age and middle age group for the latency of component on all electrodes. The young age group was however significantly different from both groups on all electrodes. There was no significant difference in the latency of the negative component recorded from the frontal channel (F3) and the positive component recorded from the occipital electrode (O1) by means of a paired t-test. The group averaged data of latency and amplitude, of the negative and positive components recorded at around 65-75 msec from the middle age and old age groups, are given in Table 5.2.

Figure 5.9:- This figure shows the group averaged data, for the same three groups to binocular flash stimulation, cursored at the latency of the P1 component. A clear P1 component, at 78 msec, is present in the old age group over the occipital and parietal regions, however, there is no such identifiable component in the middle and young age groups. At about the same latency a frontal negative response was recorded in the middle and old age groups but it was not present in the young age group.

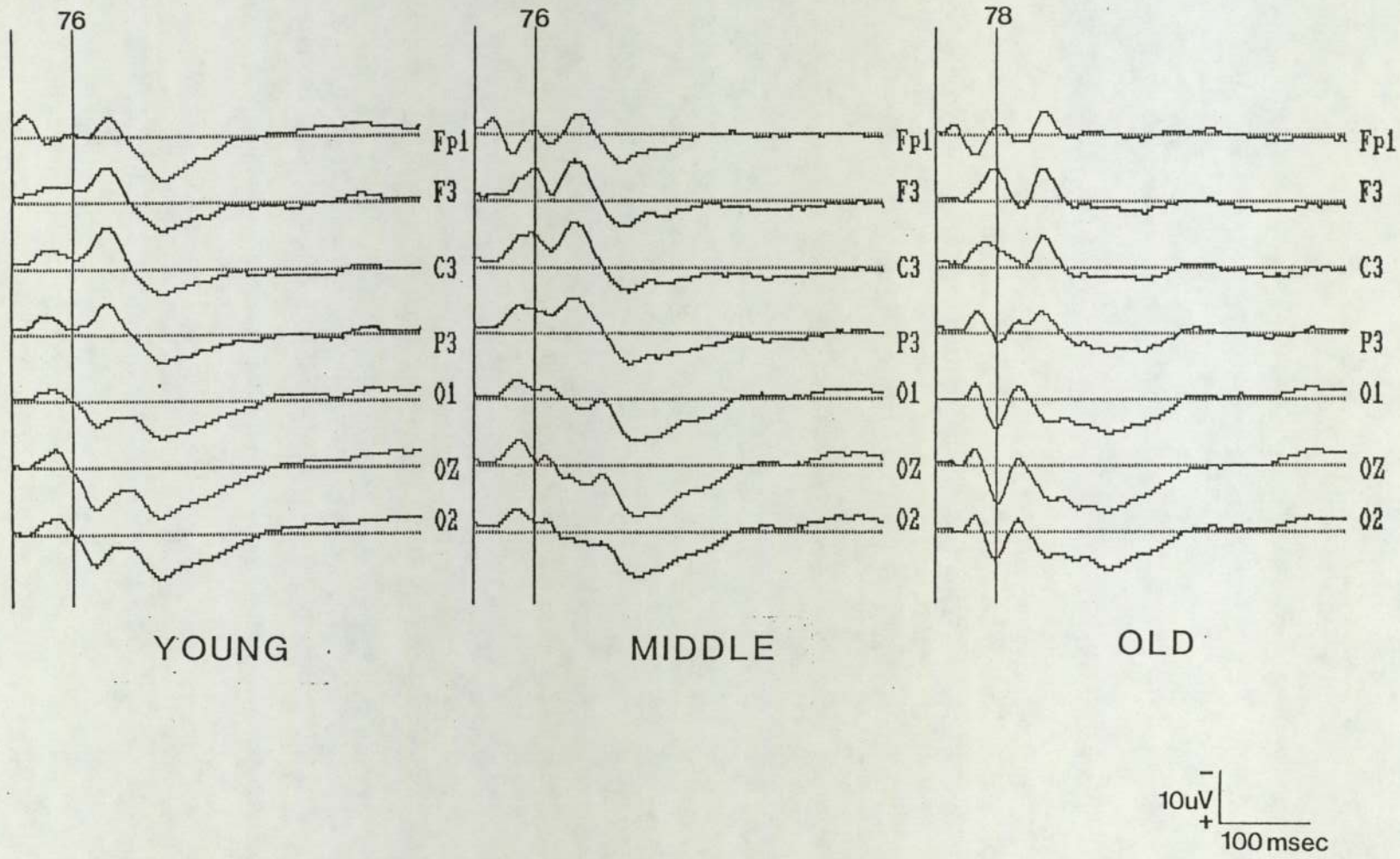
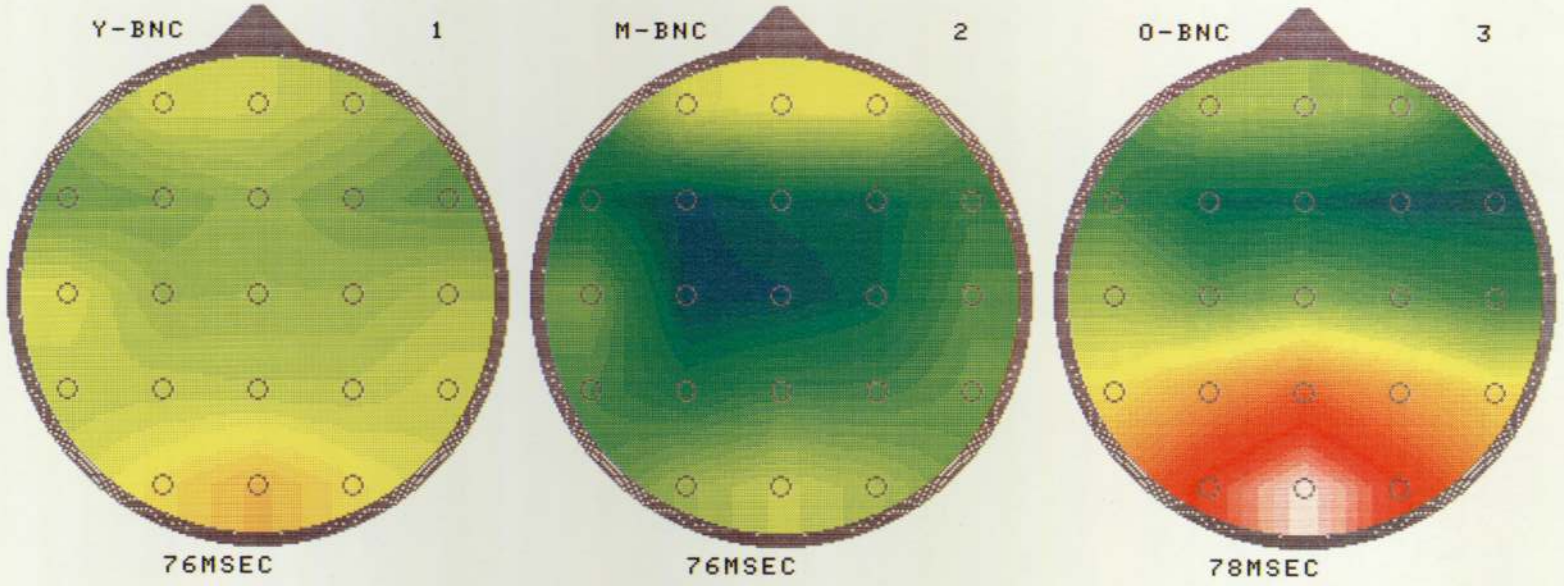

76
76
78
Fp1
F3
C3
P3
01
OZ
02
YOUNG
MIDDLE
OLD
10uV
100 msec

Figure 5.10:- This figure shows the brain maps of the group averaged data shown in figure 5.9 and illustrates how a clear P1 is only recorded in the older age group. The map of the young age group shows no component either frontally or occipitally, the map of the middle age group's data shows frontal negative activity with no occipital positive activity whilst the map of the old age group's data clearly shows both a frontal negativity and an occipital and parietal positivity.


Y-BNC
1
76MSEC
M-BNC
2
76MSEC
O-BNC
3
78MSEC
200 x200
Rectangular
-6.1
6.1
MAP
Nicolet Pathfinder TMAP

	LATENCY						AMPLITUDE				
GROUP	FP1	F3	C3	P3	O1		FP1	F3	C3	P3	O1
MIDDLE	70.29	70.67	71	71.11	76.44		-6.36	-6.59	-5.35	0.49	4.75
±1SE	1.87	1.87	2.01	3.11	2.05		0.87	0.6	0.77	1.44	1.01
OLD	78.63	74.94	72	78.32	78.89		-6.65	-6.23	-4.62	6.23	9.51
±1SE	1.72	1.84	2.74	1.13	1.59		0.58	0.44	0.54	0.76	1.22

Table 5.2:- The group averaged latency and amplitude data of the middle and old age groups for the negative and positive components recorded at about 60-75 msec to binocular flash stimulation.

The amplitude of the negative response recorded on F3 and C3 between the middle and old age groups showed no significant difference. However, analysis showed that the amplitude of the responses recorded from the older group from electrodes P3 and O1 were significantly larger ($F=20.68$; $df=1,26$; $p<0.001$; $F=6.40$; $df=1,26$; $p<0.02$ respectively) than those recorded from the middle age group.

In the old age group there is a clear and definite P1 component at the P3 electrode and the standard error of the latency values is small but interestingly much larger for the values recorded at the C3 electrode as this now becomes the electrode around which the inversion in polarity of the component occurs. In the group averaged traces of the middle age group a P1 component is not readily identifiable and the standard error of the latency value at the P3 and O1 is higher than for the prominent negative components on the frontal channels.

5.3.2 THE TOPOGRAPHY OF THE FLASH VER RECORDED WITH THE EYES CLOSED.

Although data was collected through closed eyelids, it's presentation as topograms at a moment in time becomes misleading due to the presence of alpha activity. The amount of alpha activity recorded during this experiment was probably increased by the length of time spent in preparation i.e. electrode application, setting the BNCR, as well as the subject being in a supine position, and the wearing of occluding headphones. It was concluded that the data was misleading and has been omitted from the analysis.

5.4.0 DISCUSSION

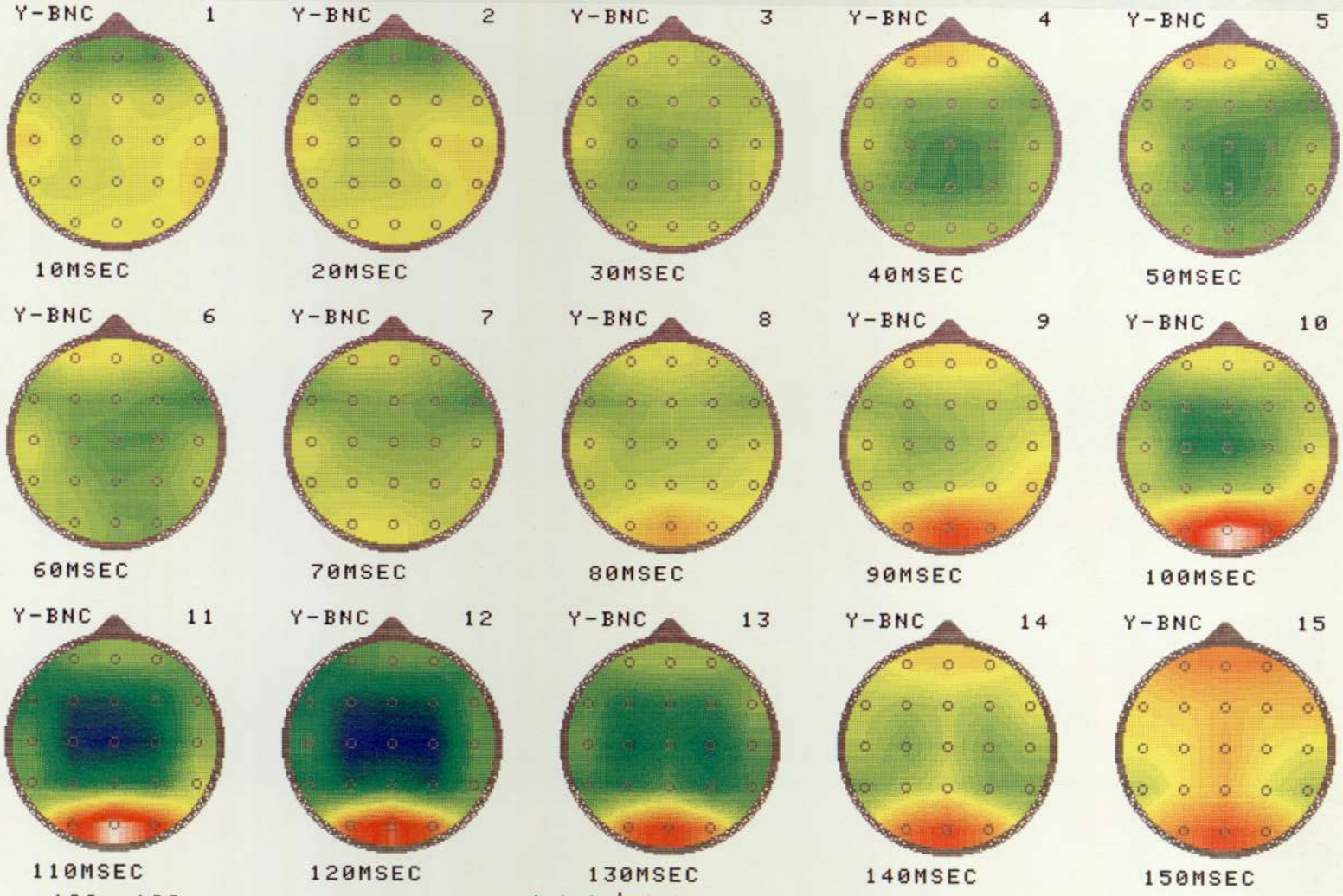
The main conclusion from this work is that when a flash VER is recorded, the frontal channels rather than being inactive actually show negative activity the morphology of which alters with age. The results confirmed earlier work that the P1 component is more readily recorded in the elderly and that the latency of the P2 component increased with age (Wright et al 1985). However, the development of the P1 component during middle age is preceded by the development of a frontal negative component of around the same latency. The group averaged data also shows that the P1 component has a more anterior distribution than the P2 component being clearly recordable over the parietal region.

The origins of the frontal negative components that occur at around the same latency as the P1 and P2 components on the occiput are unknown and the development of the earlier frontal component during middle age has not been previously described.

The presentation of the group averaged data to flash stimulation for the three age groups at intervals throughout the response enables comment on the development of the responses. A series of maps illustrating the group averaged flash responses are presented at 10 msec intervals, up to 150 msec, the time by which the evoked response has been completed in the normal subjects studied here.

Firstly, looking at negative potential, the young age group shows a bilateral negative potential at around 40-50 msec in the parietal-central region which reaches a maximum potential of around 3.4 μV (Figure 5.11). The potential then becomes more anterior in location and reduces in amplitude and by 80-90 msec there is no localised negative

Figure 5.11:- The group averaged data of the young age group to binocular flash stimulation mapped at 10 msec intervals.


Y-BNC 1
10MSEC
Y-BNC 2
20MSEC
Y-BNC 3
30MSEC
Y-BNC 4
40MSEC
Y-BNC 5
50MSEC
Y-BNC 6
60MSEC
Y-BNC 7
70MSEC
Y-BNC 8
80MSEC
Y-BNC 9
90MSEC
Y-BNC 10
100MSEC
Y-BNC 11
110MSEC
Y-BNC 12
120MSEC
Y-BNC 13
130MSEC
Y-BNC 14
140MSEC
Y-BNC 15
150MSEC
100 x100
Rectangular
-6.5
6.5
MAP
Nicolet Pathfinder TMAP

activity. A further bilateral negative potential then develops over the central and frontal regions by 110 msec, is maximal at around 120 msec, with an amplitude of about 6.50 μV. A reduction in amplitude of the potential then occurs through to 150 msec.

The middle age group shows a bilateral negative potential which begins to develop at around 40-50 msec over the parietal and central regions. The negative potential reaches a maximum at about 70 msec over the central and frontal regions with an amplitude of around 5.0 μV (Figure 5.12). A reduction in amplitude then occurs with no localised negative activity being present by 90-100 msec. Negative potential then develops over the parietal, central and frontal regions reaching an amplitude of around 7.0 μV by 120 msec, which then reduces in potential through to 150 msec.

In the old age group a bilateral parietal and central negative potential develops between 40-50 msec and reaches a maximum of around 6.0 μV over the frontal region between 70-80 msec (Figure 5.13). The negative potential subsequently reduces in amplitude and is absent by around 100 msec. At 120 msec a further negative potential starts to develop over the parietal and central regions, at around 130 msec it has reached an amplitude of 4.0 μV over the central and frontal regions and is maximal by 136 msec over the central and frontal regions with an amplitude of 5.4 μV. A reduction in negativity then occurs through to 150 msec.

The development of the occipital positive components follows a different time span. In the young age group a small occipital positive potential begins to develop at 80 msec over the occipital region and reaches a maximum at around 110 msec, the latency of the P2 component. A positive potential of reduced amplitude is recordable through to 150

Figure 5.12:- The group averaged data of the middle age group to binocular flash stimulation mapped at 10 msec intervals.

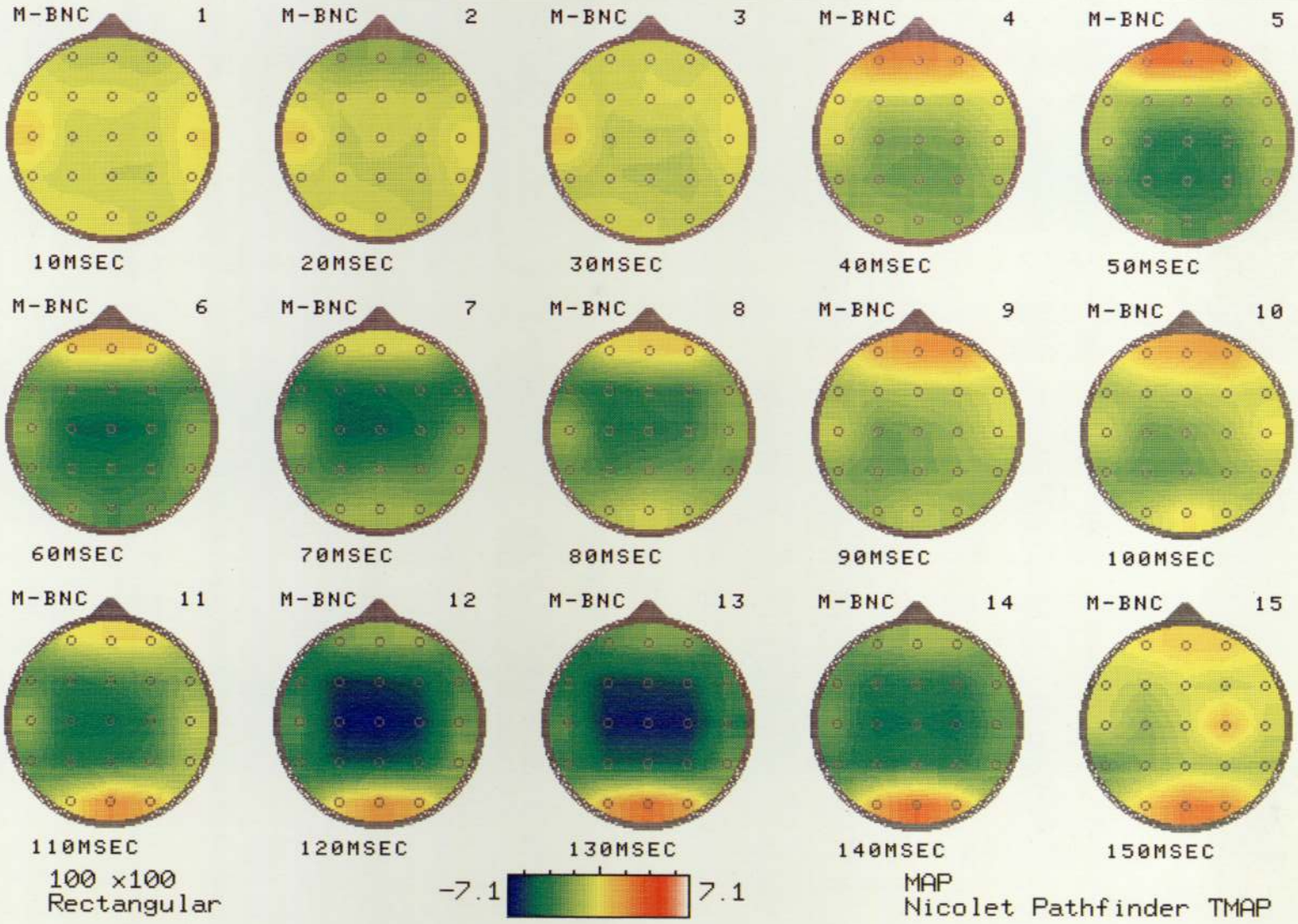
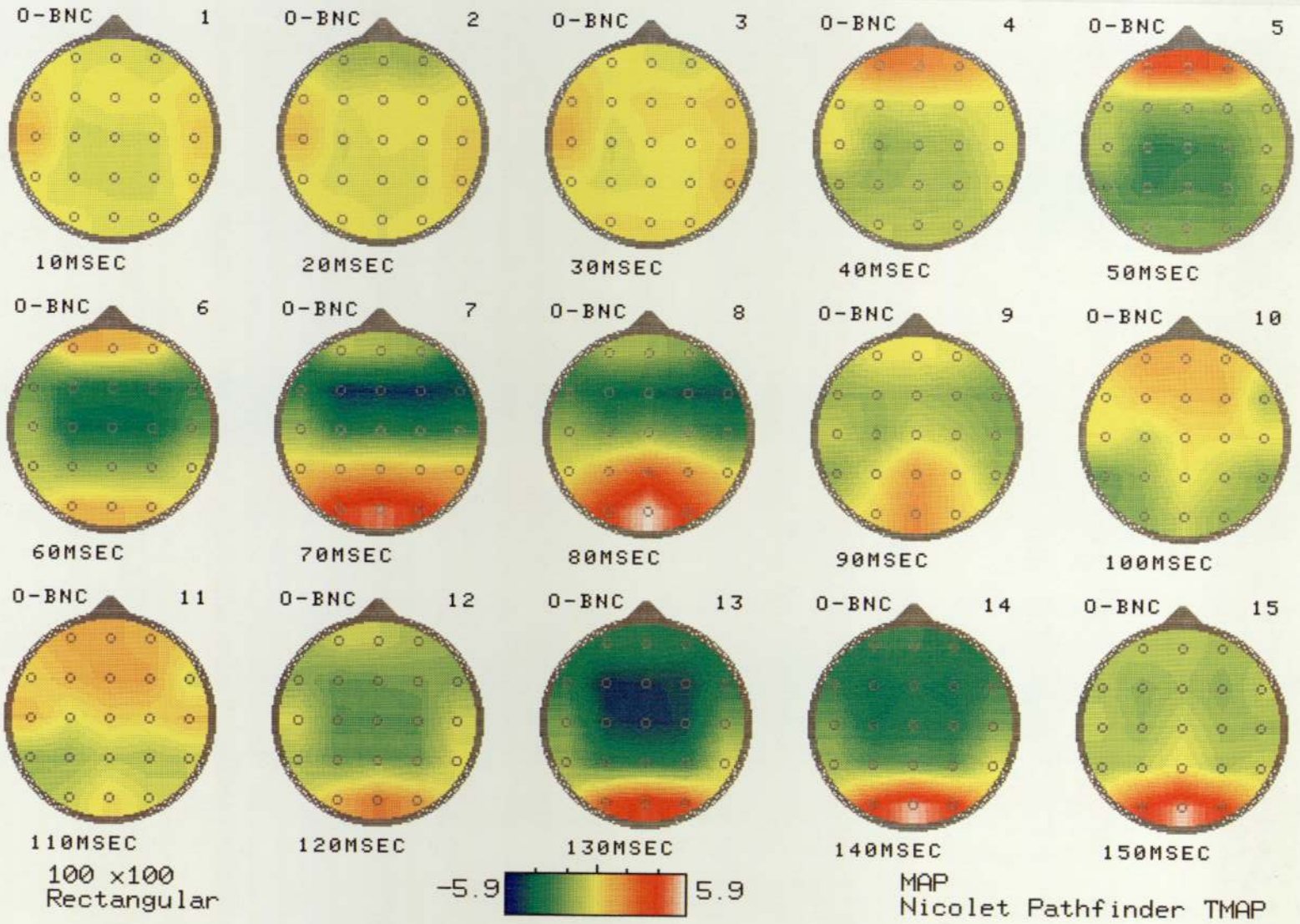

M-BNC 1
10MSEC
M-BNC 2
20MSEC
M-BNC 3
30MSEC
M-BNC 4
40MSEC
M-BNC 5
50MSEC
M-BNC 6
60MSEC
M-BNC 7
70MSEC
M-BNC 8
80MSEC
M-BNC 9
90MSEC
M-BNC 10
100MSEC
M-BNC 11
110MSEC
M-BNC 12
120MSEC
M-BNC 13
130MSEC
M-BNC 14
140MSEC
M-BNC 15
150MSEC
100 x100
Rectangular
-7.1
7.1
MAP
Nicolet Pathfinder TMAP

Figure 5.13:- The group averaged data of the older age group to binocular flash stimulation mapped at 10 msec intervals.


0-BNC 1
10MSEC
0-BNC 2
20MSEC
0-BNC 3
30MSEC
0-BNC 4
40MSEC
0-BNC 5
50MSEC
0-BNC 6
60MSEC
0-BNC 7
70MSEC
0-BNC 8
80MSEC
0-BNC 9
90MSEC
0-BNC 10
100MSEC
0-BNC 11
110MSEC
0-BNC 12
120MSEC
0-BNC 13
130MSEC
0-BNC 14
140MSEC
0-BNC 15
150MSEC
100 x100
Rectangular
-5.9
5.9
MAP
Nicolet Pathfinder TMAP

msec over the occipital region. The positive which is maximal at around 110 msec appears to develop slightly ahead of the anterior negative potential described (Figure 5.11).

In the middle age group an occipital positive component begins to develop between 100-110 msec and is maximal between 120-130 msec. In this case the frontal negative and occipital positive potentials appear to develop over the same time course. There is a reduced positive potential present over the occipital region through to 150 msec. As previously described there is no occipital positive potential associated with the earlier frontal negative potential (Figure 5.12).

In the older age group an occipital positive potential develops around 60-70 msec and is maximal between 70-80 msec (P1 component) which subsequently reduces in amplitude and is absent by 100 msec. At around 120 msec there are early signs of the development of an occipital positive component which reaches a maximum at 136 msec (P2 component) and then reduces in amplitude to 150 msec. The frontal N75 component develops prior to the occipital positive P1 component whereas the frontal N120 component appears to develop at around the same time as the occipital positive P2 component (Figure 5.13).
In all cases as the occipital positive potential increases in amplitude the area of negativity becomes more anterior.

In all three age groups a small amplitude positive potential is present at around 40-50 msec over the frontal region. This positivity is believed to be the b-wave of the ERG and will be investigated in the following chapter. The middle age group shows a small amplitude frontal positivity at around 90-100 msec. Although, examination of the brain

maps would suggest that the middle age group exhibits a frontal positive component at around this latency, examination of the traces, shown in Figure 5.6, show that the positivity is the result of the trace drifting below the baseline.

There is evidence in the literature that the frontal channels are not inactive whilst recording a flash VER. Gastaut & Régis (1965) looked at the waveforms recorded from a chain of electrodes running from the nasion to the inion, all referred to the chin, and showed that the morphology of the waveform was dependent upon the electrode location (Figure 5.14). The central and parietal electrodes showed a negative component at around the same latency as the positive P2 component on the occipital lead. This concurs with our results for the three age groups. They reported that the frontal channels were dominated by ERG which is hardly surprising considering that the spread of the ERG has been demonstrated as far as the rolandic fissure (Rubinstein & Harding 1981). However, the latency of the b-wave of the ERG is earlier than the P1 component or the N75 component, and is, of course, positive.

In 1964, Kooi & Bagchi reported the presence of a vertex sharp wave (V wave), a negative potential at around 140 msec (range 120-160 msec) which was maximum in size around the central region. In 1968, Kooi et al recorded a second frontal negative potential which they termed the frontal or F wave. These recordings were made to linked ear reference on subjects varying in age from 17-72 years. Almost half of the subjects had the frontal wave which had a latency range of 150-200 msec, with a mean of 176 msec. They postulated that the frontal wave was of neural origin and did not originate from the eye. It is possible that the negative vertex wave (V wave) of Kooi &

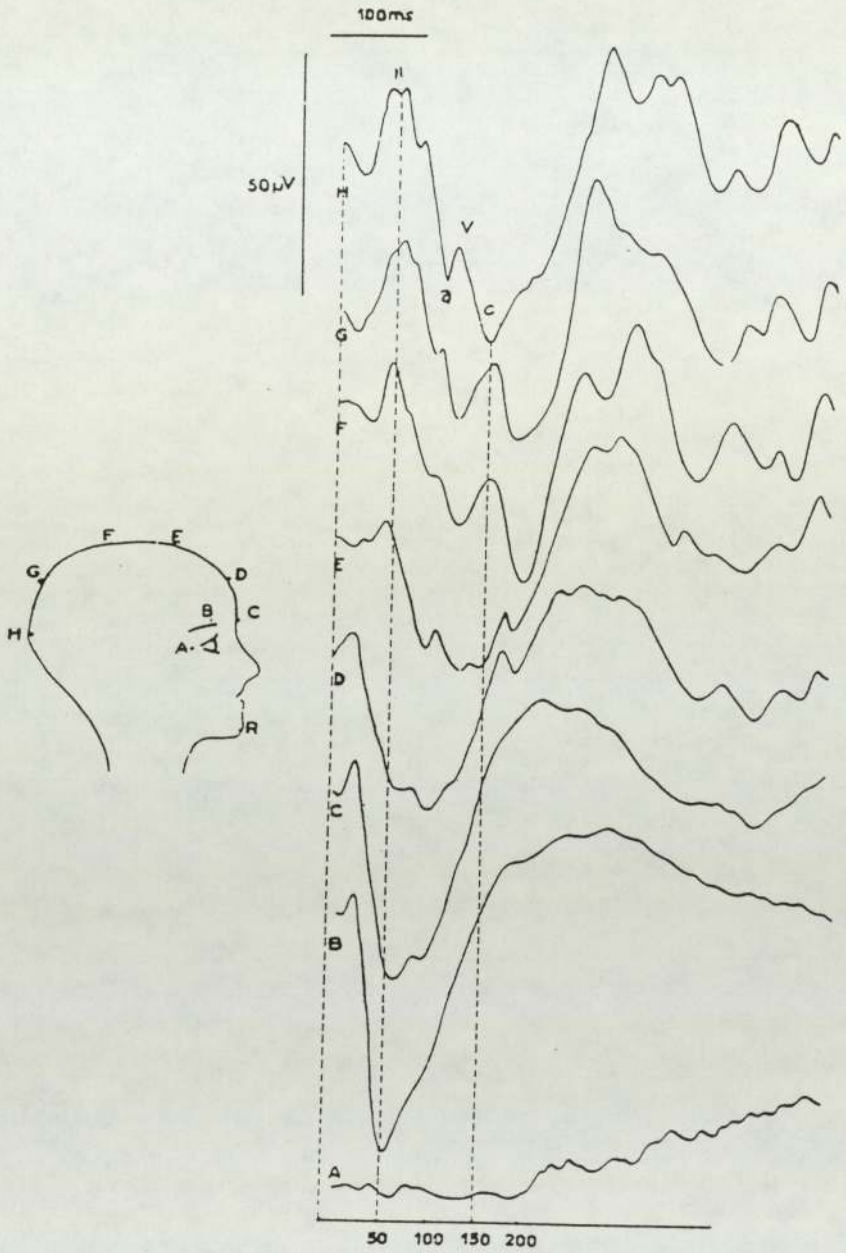


Figure 5.14:- This figure shows the morphology of the waveforms to flash stimulation recorded from a chain of electrodes from the nasion to the inion referred to the chin. It shows a negative component on the electrodes G and F at the same latency as the positive P2 component on the occipital channel H. (after Gastaut & Régis 1965).

Bagchi (1964) equates with the second frontal negative i.e. the N120 of the recordings presented here. An F wave of the latency they state was not recorded in any of the groups.

Allison et al (1977) looked at the scalp topography of the flash VER on subjects aged 18-39 years. They used a contralateral earlobe reference, the stimulus was presented in Maxwellian view to the right eye, subjects were dark adapted for thirty minutes prior to testing and an average of 64 repetitions was recorded. They were able to identify twenty two components of the flash VER. Frontal negative or positive components prior to 80 msec they proposed originated in the ERG, whilst those components after 80 msec were of neurogenic origin. The frontal potentials they recorded were an N20, P50 and a P65 component on electrodes Fp1 and Fp2. They suggested that the N20 component was part of the ERG a-wave, the P50 component was part of the ERG x-wave and the P65 component was part of the ERG b-wave. An N80 component was occasionally recorded at the outer canthus electrode and they thought that this may be part of the ERG after potential or was perhaps myogenic in origin. They also were unable to record the F wave of Kooi et al (1968).

Several authors have shown the presence of a frontal negative component (N100) at about the same latency of the positive occipital P100 component of the pattern reversal response (Asselman et al 1975, Spitz et al1986, Shih et al1988) (Figure 5.15). Two studies used a non-cephalic reference as an alternative reference site to either single or linked mastoids. The non-cephalic reference used in one study was the 5th cervical vertebra (CV5) (Spitz et al 1986) whilst in the other the 1st thoracic vertebra (T1) was used (Shih et al1988). The results of both studies showed that the latencies of the P100 and the N100 components can be, but are not always, synchronous. Inversion in

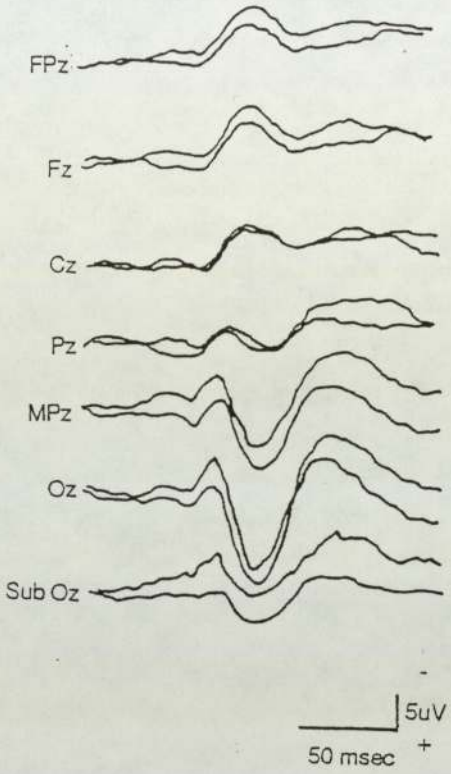


Figure 5.15:- This figure shows the response to pattern reversal stimulation recorded with a non-cephalic reference. A negative component is recorded on the frontal channels at around the same latency as the positive occipital component. (after Spitz et al 1986).

polarity of the component was found to occur most commonly around the central and parietal regions, the exact location varing from individual to individual (Shih et al 1988). These results are similar to those found in this study as regards to the region of the brain around which the inversion in polarity of the components was found to occur. This may be related to the presence of the Rolandic fissure in the underlying area.

In their discussion Spitz et al (1986) put forward various suggestions as to the origin of the frontal negative component of the pattern reversal response. They did not believe that the P100 and N100 components represented opposite ends of the dipole generator of the pattern reversal VER, as the components were not always synchronous. The data presented here shows that although there is no significant difference in latency between the N75 component recorded on F3 compared to the P1 component recorded on O1 or the N120 component recorded on F3 compared to the P2 component recorded on O1, the two components are not always synchronous. The fact that the components are not synchronous would suggest that they do not represent separate ends of dipole generators, however, it cannot be excluded as an explanation as small changes in latency could be the result of other underlying brain activity advancing or retarding the peak of the potential. Spitz et al (1986) put forward the suggestion that the frontal negative component of the pattern reversal response is a far field effect. However, if it was the result of a far field effect one would have expected the component to have been a constant feature wherever the recording electrode was on the scalp. A second alternative they proposed is that the two components represent separate temporal processing of visual information after its arrival at the primary visual cortex. This would account for the finding that the two components are not always synchronous.

The separate development of the two frontal negative components, the N75 and N120, of the flash VER suggests that they may originate from different anatomical sites and although it is possible that the N120 represents a separate end of the dipole involved in the generation of the flash VER P2, this is unlikely in the case of the N75 component. The fact that the development of this component precedes the development of P1 during the life span suggests that either this component arises independently or that the P2 component in the middle age group somehow camouflages the presence of a P1 component.

The choice of reference site plays an important role in the morphology of evoked responses. This was shown with respect to the pattern reversal evoked potential by Michael & Halliday (1971) , Spitz et al (1986) and Shih et al (1988). Michael & Halliday (1971) recorded pattern reversal responses to both upper and lower field stimulation with respect to both earlobe and midfrontal references. The responses recorded to lower field stimulation referred to either reference had very similar morphologies except that the amplitude of the response was greater when a midfrontal reference was used. The polarity of the responses recorded on the posterior channels to upper field stimulation, however, was dependant upon the reference site used. The earlobe reference gave a negative peak whereas the midfrontal a positive peak. They concluded from this that either the earlobe was making a positive contribution or the midfrontal a negative contribution to the recorded responses.

The implication of using an Fz or central electrode as the reference site for the recording of pattern reversal VERs are discussed by both Spitz et al (1986) and Shih et al (1988). As previously stated both groups have shown that the frontal Fz electrode is not inactive but records negative activity with pattern reversal stimulation. Thus when the P100 and

N100 components are recorded at the same latency, an enhancement of the P100 component results from the use of an Fz reference. When the two recorded components are not at the same latency, then the use of a frontal reference can result in a broad or W shaped P100 component. The absence of a P100 component over the occipital region, combined with the presence of a frontal negative N100 component, can result in the appearance of a P100 component should an Fz reference be used.

The choice of reference site is a particular problem in the recording of the flash VER. Many studies (Gastaut & Régis 1965, Allison et al 1977, Harding & Rubinstein 1981) have shown that it is almost impossible to chose a site which is unaffected by either the flash ERG or the flash VER. However, it is usually assumed that whichever reference site is chosen this reference site will have a consistent relationship to the active electrode site over the age range. If this statement is not true then obviously the apparent components recorded at different ages at the active electrode may not be originating from that site at all but from the reference electrode instead.

It is common practice in electrophysiology to record the flash VER with reference to either the midfrontal electrode (Fz) (Halliday et al 1972, Mushin et al 1984, Wright et al 1984) or the central electrodes C3 and C4 (Harding & Crews 1982). It is possible to convert the group averaged data presented in Figure 5.6 and Figure 5.9 as if it had been recorded from an Fz reference (Figures 5.16, 5.17, 5.18, 5.19). The resulting group averaged traces of the young age group show a clear well defined P2 component at 112 msec. The group averaged traces of the middle age group show a P1 component at 74 msec and a P2 component at 130 msec, whilst the group averaged traces of the older age group shows a P1 component at 76 msec and a P2 component at 132 msec.

Therefore, the study above would suggest that the use of a midfrontal (Fz) electrode as the reference site for a flash VER could produce an artificial P1 component in the middle age group and an enhancement of the component in the elderly, in addition to an enhancement of the P2 component in all subjects. Since the negative activity on the central electrodes C3 and C4 was of the same order as that on the frontal electrodes the same rationale should apply to their use as reference sites.

Figure 5.16:- The same group averaged data, for the three groups to binocular flash stimulation, displayed as if recorded referred to a midfrontal (Fz) reference. A well defined P2 component is clearly visible over the occipital region in all three age groups.

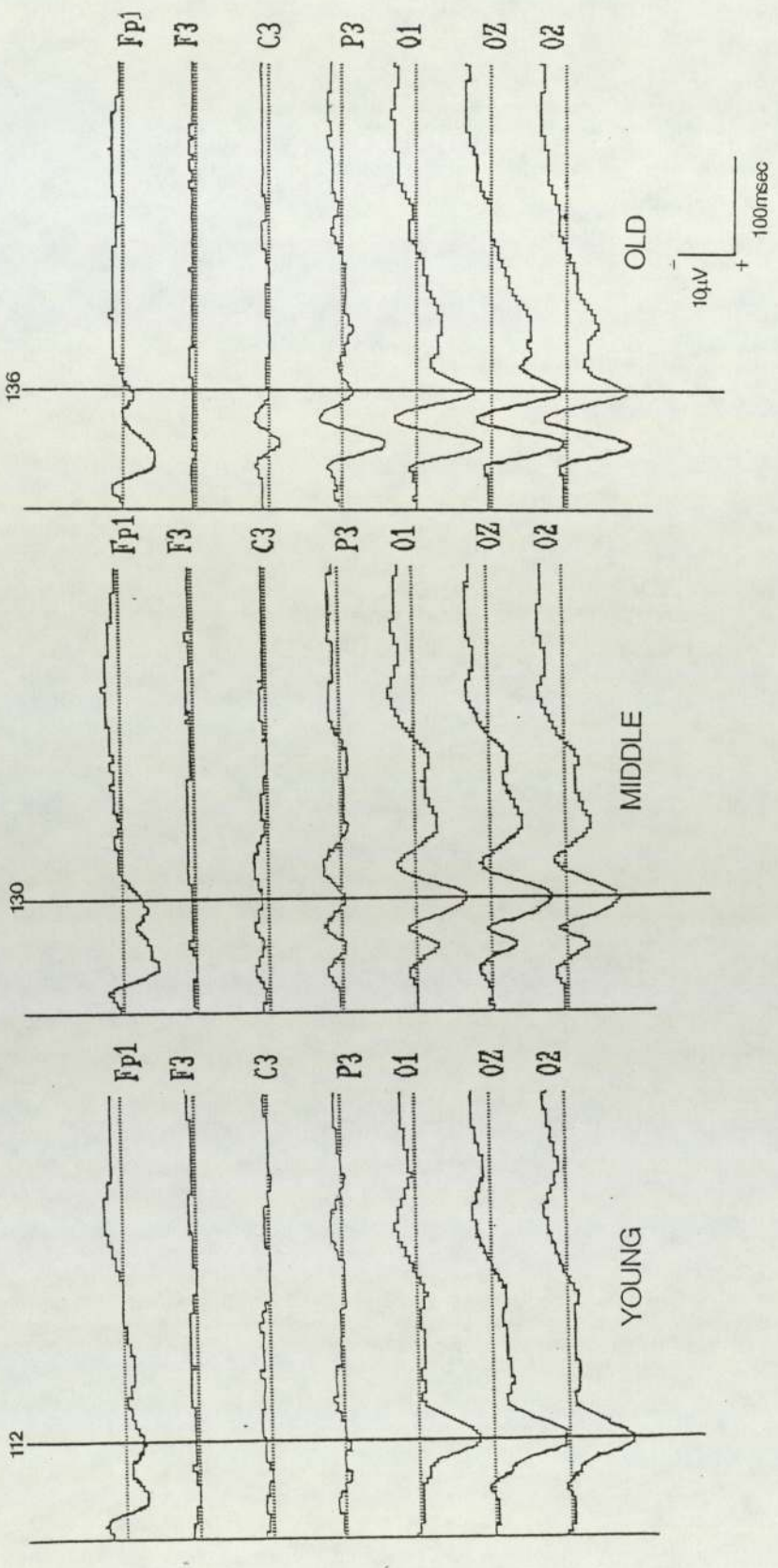
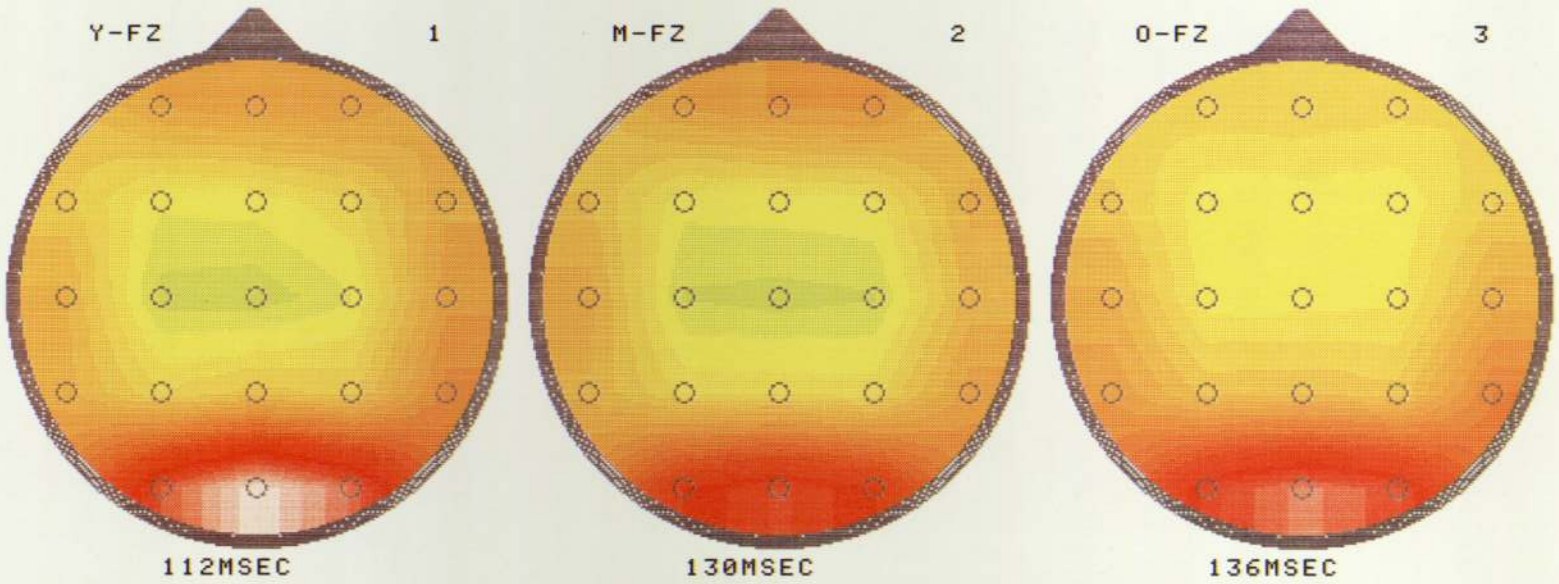
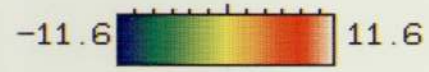

112
130
136
Fp1
F3
C3
P3
O1
OZ
O2
YOUNG
MIDDLE
OLD
10μV
100msec

Figure 5.17:- This figure shows the brain maps of the group averaged data in figure 5.16. All three age groups show a well defined occipital positive component confined to the occipital region.



200 x200
Rectangular



MAP
Nicolet Pathfinder TMAP

Figure 5.18:- The same group averaged data, for the three groups to binocular flash stimulation, displayed as if recorded referred to a midfrontal (Fz) reference. In the young group it can be seen that only the P2 component is apparent. In the middle age group the use of a frontal electrode as reference has produced an apparent P1 component on the occipital derivation due to the N75 component at the reference. In the old age group the use of a midfrontal reference has exagerated the P1 component.

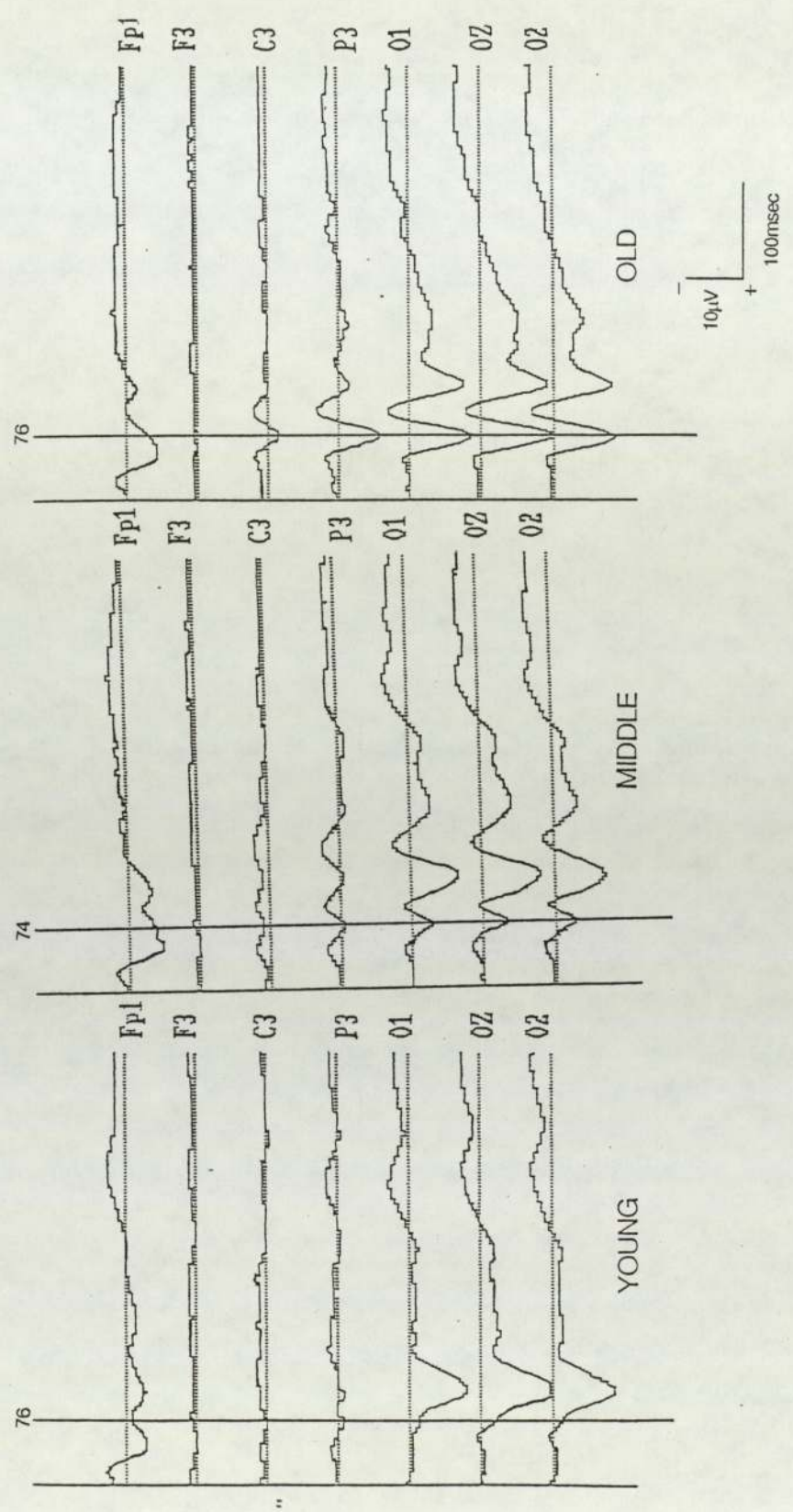
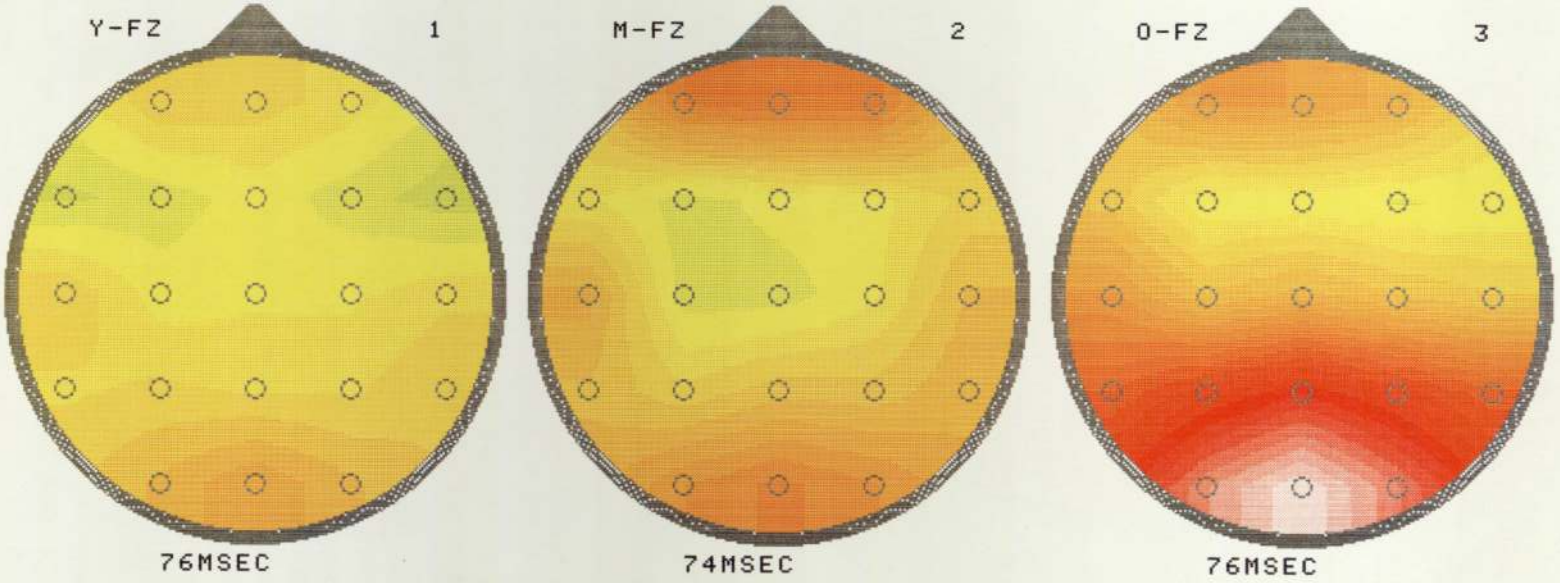

Fp1
F3
C3
P3
O1
OZ
O2
76
74
YOUNG
MIDDLE
OLD
10μV
100msec

Figure 5.19:- This figure shows the brain maps of the group averaged data shown in figure 5.18. It illustrates that when the data to binocular flash stimulation is displayed as if referred to an Fz reference there is no P1 component in the young, a small occipital positivity in the middle age group and an enhanced occipital and parietal positivity in the old age group.


Y-FZ
1
76MSEC
M-FZ
2
74MSEC
O-FZ
3
76MSEC
200 x200
Rectangular
-10.8
10.8
MAP
Nicolet Pathfinder TMAP

5.5.0 SUMMARY

In summary, during the recording of a flash VER the frontal channels rather than being inactive actually show negative activity the morphology of which alters with age. It has been shown that an occipital P2 component can be recorded across the age span with an equally recordable frontal negative component at around the same latency (N120). However, the occipital P1 component is more readily recorded in the elderly with an equally recordable frontal negative at around the same latency (N75). The development of the P1 component during middle age is proceded by the development of a frontal negative at around 75 msec. The young age group do not demonstrate either a P1 or N75 component. The N120 component develops at about the same latency as the P2 component whereas the N75 component develops earlier than the P1 component during the response. The origin of the frontal negative components are unknown and will be investigated in the following chapter.

The P1 and P2 components of the flash VER differ not only as regards their presence across the age range but also in their topography. The data shows that the P1 component has a more anterior distribution being recorded over both the parietal and occipital regions whereas the P2 component is confined to the occipital region.

This study would suggest that the use of the midfrontal (Fz) or central electrodes (C3 &C4) as a reference site for the recording of a flash VER may produce an artificial P1 component in the middle age group and an enhancement of the component in the elderly. Either of these reference sites will also enhance the amplitude of the P2 component.

CHAPTER 6

INVESTIGATION OF THE FRONTAL NEGATIVE COMPONENTS OF THE FLASH VISUAL EVOKED RESPONSE.

6.1.0. INTRODUCTION.

Although the recording of the negative component on the frontal channels at around 120 msec may have been anticipated from the literature, the recording of an earlier negative component was an unexpected finding. The origins of the frontal negative components are, as previously discussed, unknown. Before making any suggestions as to their origin, it was important to rule out any contributions arising from the electroretinogram (ERG) or the balanced non-cephalic reference (BNCR).

The photopic, i.e. cone mediated, ERG consists of a negative a-wave with a latency of about 15 msec, followed by a positive b-wave at about 40 msec (Rubinstein & Harding 1981). A dark adapted, i.e. rod mediated, ERG has an a-wave at a latency of around 25 msec and a b-wave at around 49 msec (Wright et al 1985, Ikeda 1987) (Figure 6.1). An ERG recorded on the frontal or central channels would have to be a volume conducted response. It is unlikely that the negative component recorded on the frontal or central channels at either 75 msec or 120 msec is a volume conducted a-wave, given that the initial a-wave latency at the eye is around 20 msec. A volume conducted b-wave response would result in a positive component rather than a negative component, as recorded here. Rubinstein & Harding (1981) found that the a-wave became

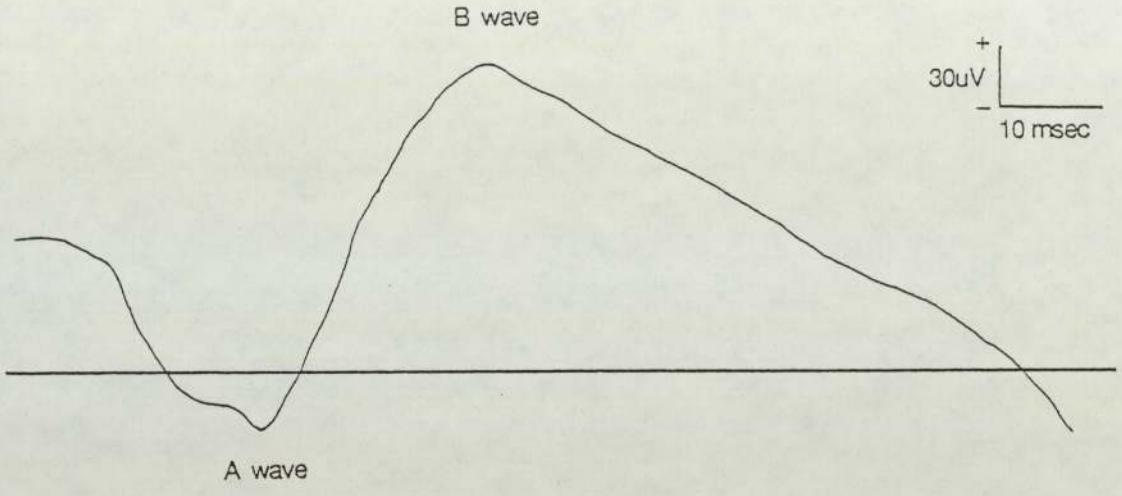


Figure 6.1:- Morphology of a typical dark adapted ERG (after Wright et al 1985).

unrecordable sooner than the b-wave, as the distance of the recording electrode increased from the eye. They found that an a-wave was not recordable at electrode F4, whereas a low amplitude b-wave was present, with a latency of around 37 msec. They used a Cz reference, a stimulus rate of 6/sec and the filters were set at 66 to 700 Hz. Although this would suggest that ERG involvment is unlikely, all these studies have used ERG recording parameters i.e. wide filter settings from 0.3 up to 700 Hz and higher intensities of stimulation. Therefore, an experiment was performed, using the filter settings and intensity of stimulation employed throughout the present VER study to eliminate the possibility of any ERG involvment in the recording of the two frontal negative components during flash stimulation.

To ensure that the negative components recorded were not a consequence of the use of the BNCR as a reference site, recordings were made using alternative reference sites. In addition, the possibility was investigated that the frontal negative components were a reflection of a spread of positive activity from the occipital region to the sterno-clavicular electrode of the BNCR.

Finally, to ensure that the previously unreported earlier negative component was not purely a general visual response as a function of age and was only related to flash stimulation, evoked responses were recorded to both pattern reversal and pattern onset/offset stimulation. As reported in the previous chapter, several authors have shown the presence of a frontal negative component (N100) at about the same latency of the positive occipital P100 component of the pattern reversal response (Asselman et al 1975, Spitz et al1986, Shih et al1988). The age of the normative subjects in the study of Spitz et al (1986) varied from 7-86 years. Although the subjects had a wide age range, there was no report of changes in the wave morphology or of component identification with age.

6.2.0 The ERG and Monocular Stimulation Study.

6.2.1. Method

Flash ERGs were recorded from 9 subjects who ranged in age from 22 years to 58 years. A chain of four electrodes were attached by tape and referred to the balanced non-cephalic reference (BNCR). The electrodes were placed just under the lower lid and just above the eyebrow, in line with the centre of the pupil when with the subject was looking straight ahead. An electrode was placed at Fz and midway between Fz and the supra-orbital electrode. The electrode placement is shown in Figure 6.2. The four channel evoked potential programme of the Biologic Brain Mapping System was used. The high and low pass filters were set at 0.3 and 30 Hz respectively, stimulation was provided by the Medelec OS5 photostimulator flashing at 1.1 Hz at intensity 2, the skin electrode resistance was reduced below 5 kΩ and the recordings were made with the subjects in a supine position. An average of 64 repetitions were recorded from the open right eye with the left eye occluded.

The subjects in the older age group, used for the study in Chapter 5, received monocular flash stimulation to the right eye, the response of which was mapped. The recording parameters and set up were as for the study reported in Chapter 5, section 5.2.0.

6.2.2. Results

For all subjects an ERG was recorded from the electrode placed at the lower lid margin with the a- and b-waves clearly visible. The mean latency of the a-wave at intensity 2 was

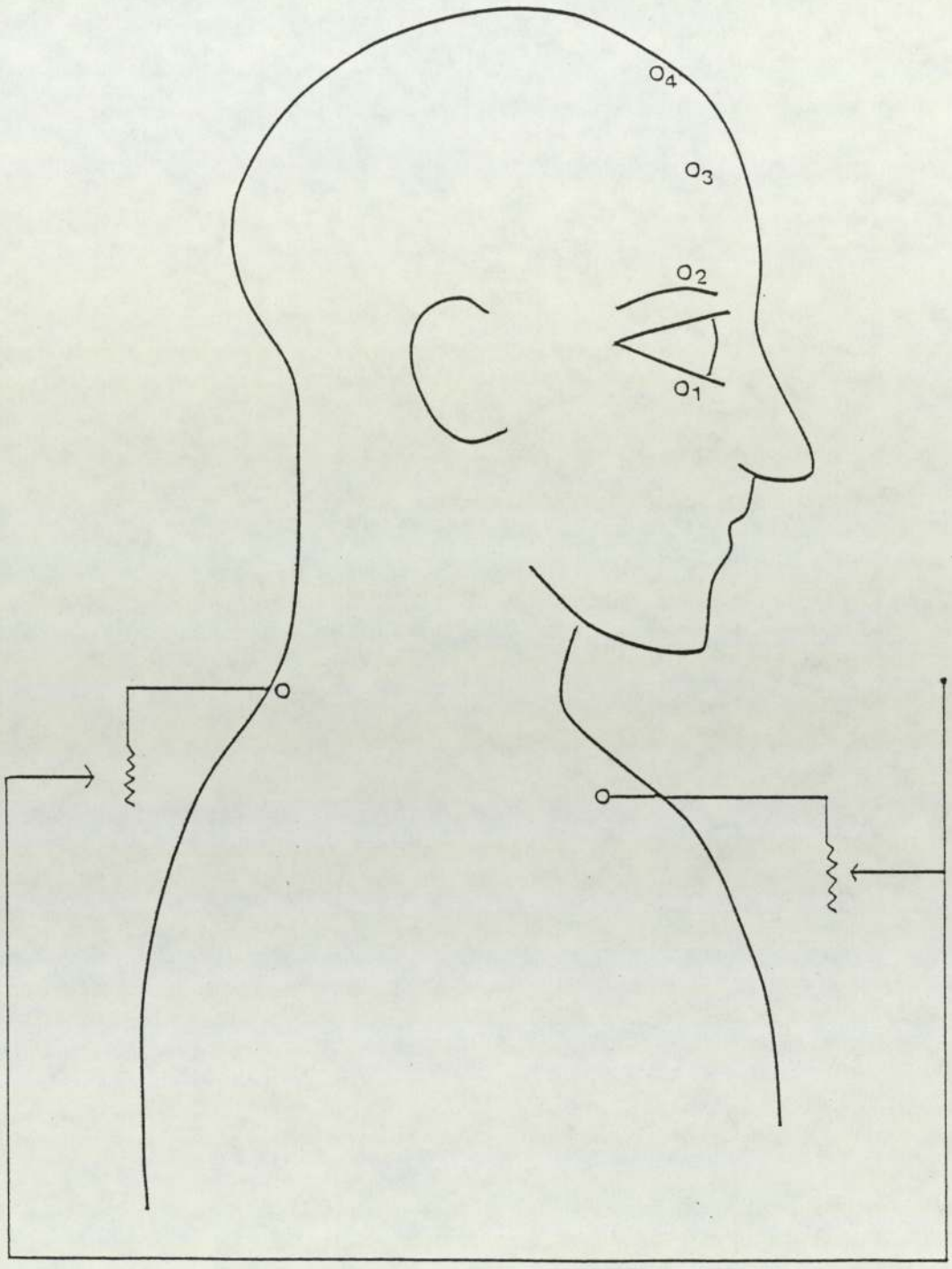


Figure 6.2:- The electrode montage used in the ERG study.

21.78 msec (±1.20) and the mean latency of the b-wave was 55.11 msec (± 5.84). ERGs were recorded at intensity 8 from four subjects and the mean latency of the a-wave was 20.50 msec (±1.00) and the mean latency of the b-wave was 48.00 msec (± 2.83). The response recorded from the three younger subjects showed a clear a- and b-wave, of some what reduced amplitude, from the electrode above the eyebrow. There were no clear components recorded from the electrode placed midway between the supra-orbital electrode and the Fz electrode. However, on the Fz electrode the negative N120 component is clearly identifable (Figure 6.3). In subjects from the middle aged group the a- and b-waves were still present on the electrode above the eye. In some cases there were signs of the N75 component. However, this component became more apparent and of greater amplitude as the recording electrode approached the Fz location (Figure 6.4).

The group averaged traces of the data from the old age group who received monocular flash stimulation to the right eye are shown in Figure 6.5. The N75 and N120 components of the response were bilateral and of equal amplitude. The mean latency of the N75 component on the F3 elctrode was 74.38 msec (± 7.87) compared with 73.88 msec (± 7.74) on the F4 electrode. The amplitude of the component was 4.38 μV (± 1.92) on electrode F3 and 4.67 μV (± 2.11) on electrode F4. There were no significant differences between the latencies or amplitudes of the N75 components recorded on electrodes F3 and F4. The latency of the N120 component was 135.29 msec (±8.29) on electrode F3 and 135.57 msec (±9.19) on electrode F4. The amplitude of the component was 7.63 μV (± 3.50) on electrode F3 compared with 7.54 μV (± 2.81) on electrode F4. There were no significant differences between the latencies or amplitudes of the components recorded on electrodes F3 and F4.

Figure 6.3:- Traces from three young individuals. Trace 1 from electrode 1 below the eye clearly showing an ERG. Trace 2 recording from electrode 2 showing a low amplitude ERG. Trace 4 from the electrode at Fz shows a clear N120 component. Trace 3 from electrode 3 shows no clear components.

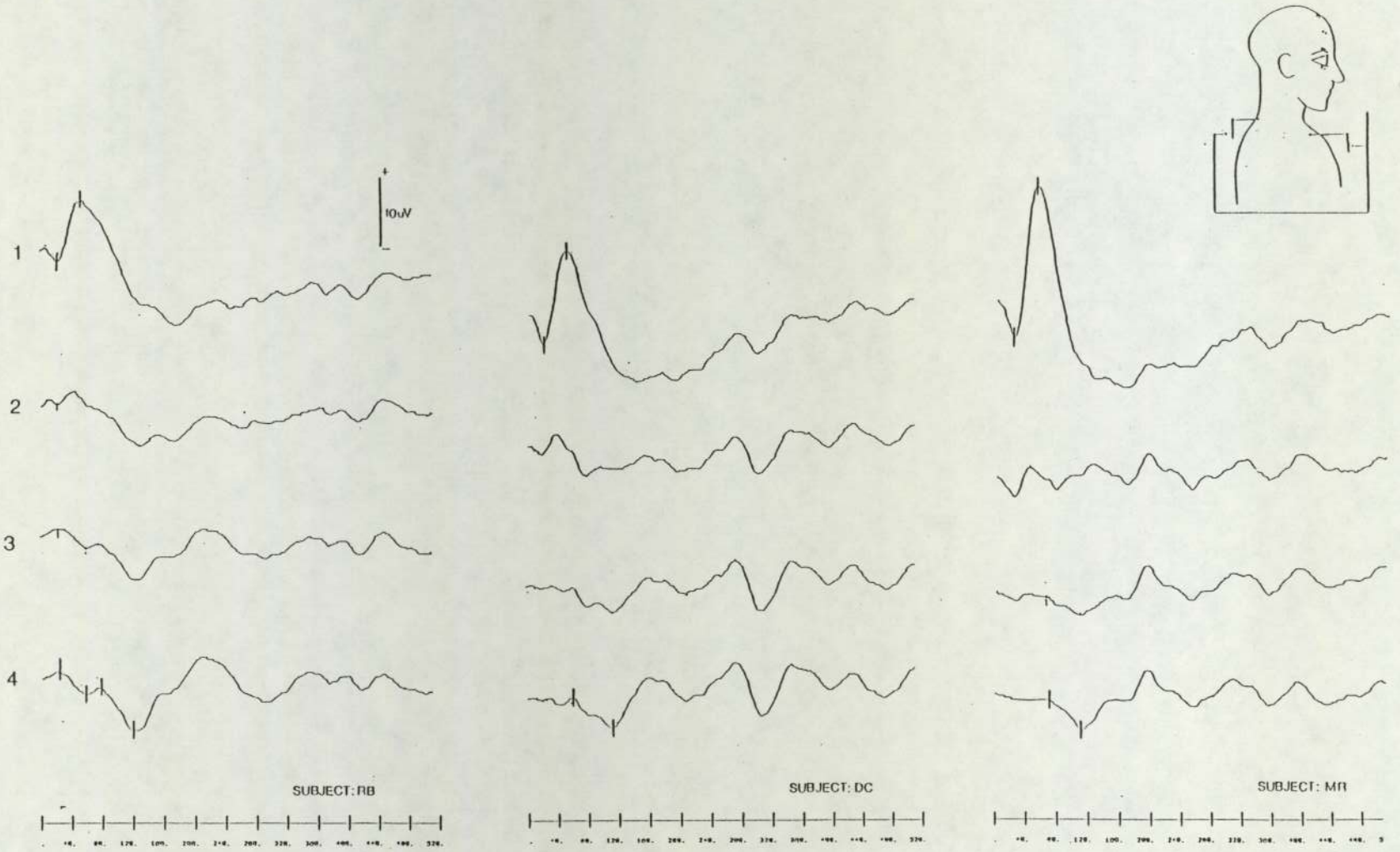
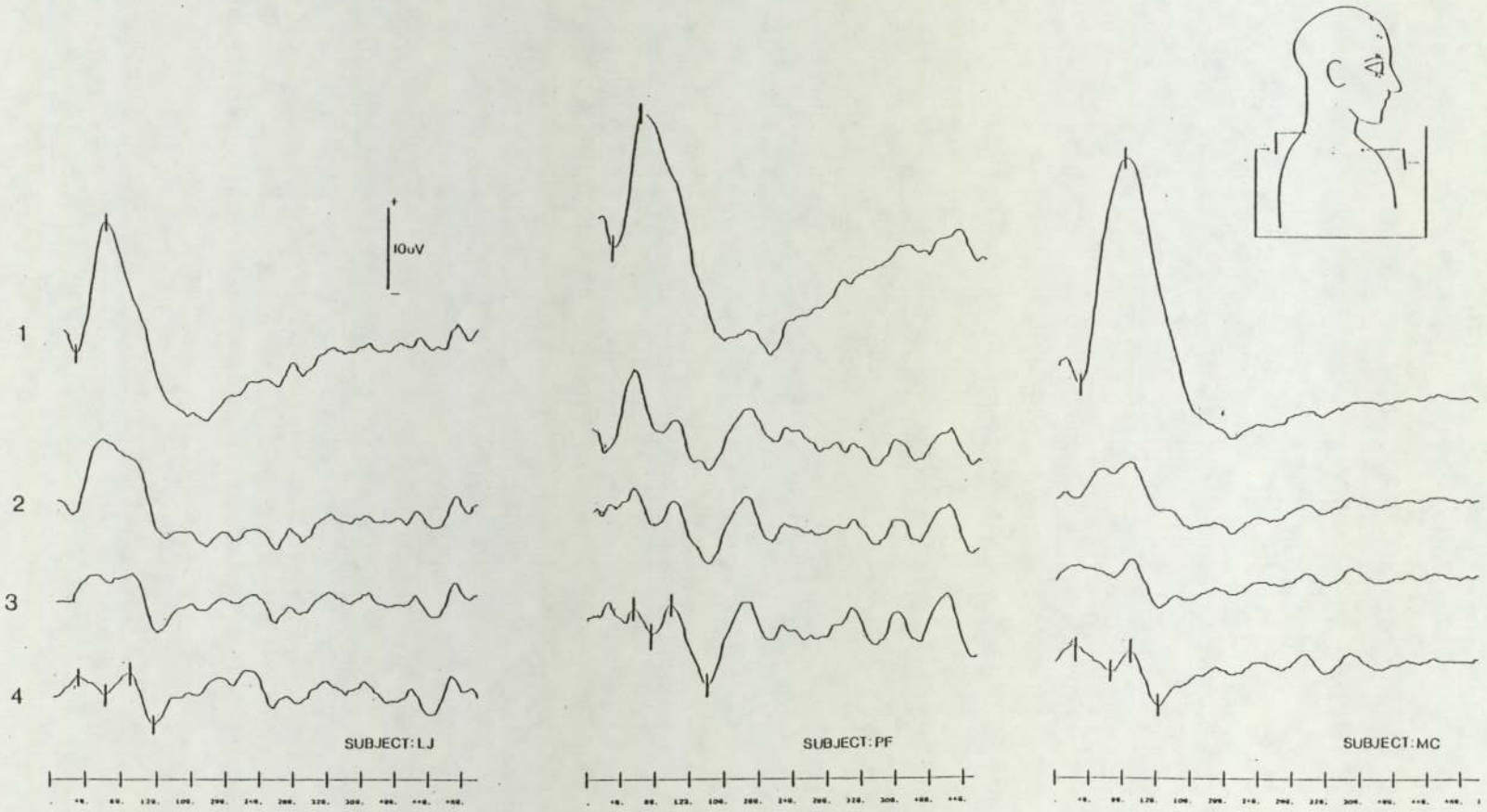

10uV
1
2
3
4
SUBJECT: RB
SUBJECT: DC
SUBJECT: MR

Figure 6.4:- Traces from 3 older subjects. Trace 1 clearly shows an ERG in all 3 subjects. Trace 2 still shows an ERG of lower amplitude. Trace 3 shows early signs of N75 and N120 components which are of greater amplitude on trace 4, recorded from the Fz electrode.


10uV
1
2
3
4
SUBJECT: LJ
SUBJECT: PF
SUBJECT: MC

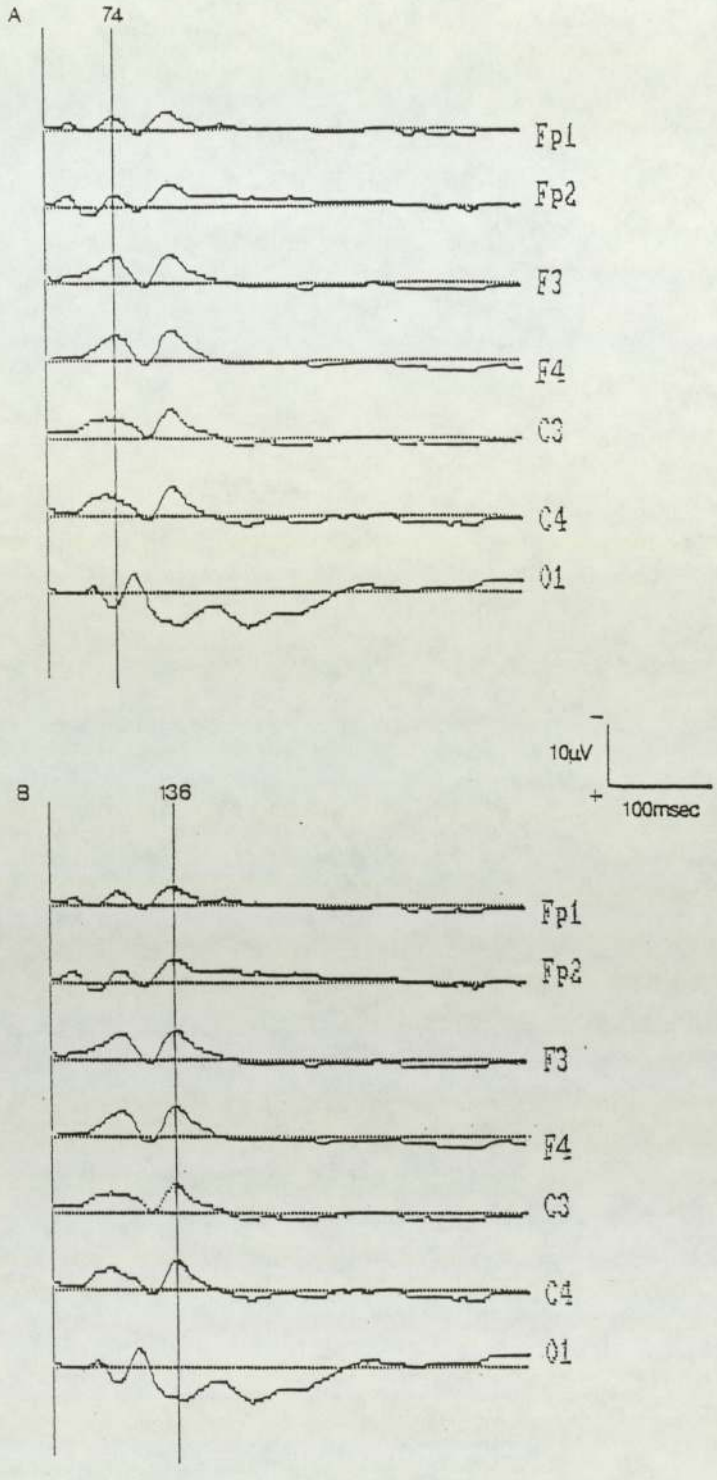


Figure 6.5:- Group averaged traces from the old age group who received monocular flash stimulation to the right eye. A) Traces cursored at 74 msec, the mean latency of the N75 component. B) Traces cursored at 136 msec, the mean latency of the N120 component.

The involvement of the ERG can be clearly illustrated by the presentation of the group averaged data for right eye stimulation at 6 msec intervals (Figure 6.6). The maps at 18 msec and 24 msec show low amplitude negative activity in the region of electrode Fp2, which has disappeared by 30 msec. By 36 msec there are early signs of positive activity over electrode Fp2 and to a lesser extent Fpz, this activity being most prominent on the maps at 42 msec and 48 msec. The electrodes at Fp2 and Fpz are isopotential by 60 msec. It is thought that the early negative potential over Fp2 is part of the ERG a-wave, and the positive potential over the Fp2 and Fpz electrodes are part of the ERG b-wave. This would confirm the findings of Allison et al (1977). The two responses described are clearly asymmetric between hemispheres and originate from the region of the right eye. The N75 component of the flash VER, however, appears initially of small amplitude at around 42 msec in the central region and is bilateral. As the occipital positive potential develops the maximum amplitude of the negative potential is recorded over the frontal region.

The group averaged data for binocular stimulation for this age group is presented in the same format (Figure 6.7). It can be seen that the development of the N75 component is virtually identical, whereas the ERG involvement described above is now bilateral. Attention should be paid to the scaling used in these two figures. The scale varies for each individual map in order to show the very small potentials present at the different moments in time.

Figure 6.6:- Maps at 6 msec intervals, of the group averaged data to monocular right eye stimulation, as far as the latency of the N75 and P1 components.
N.B. Each map has its own individual scale of amplitude.

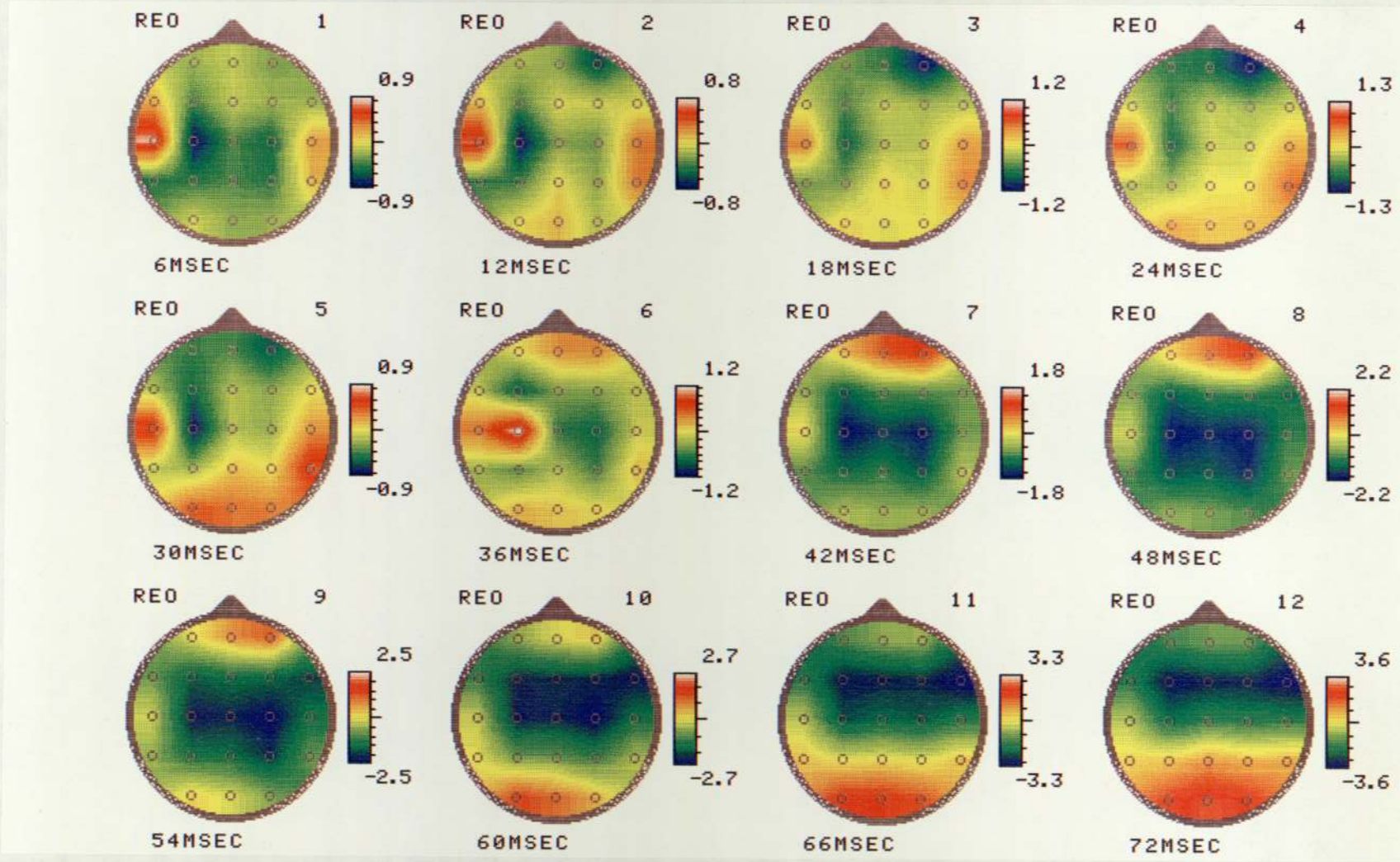
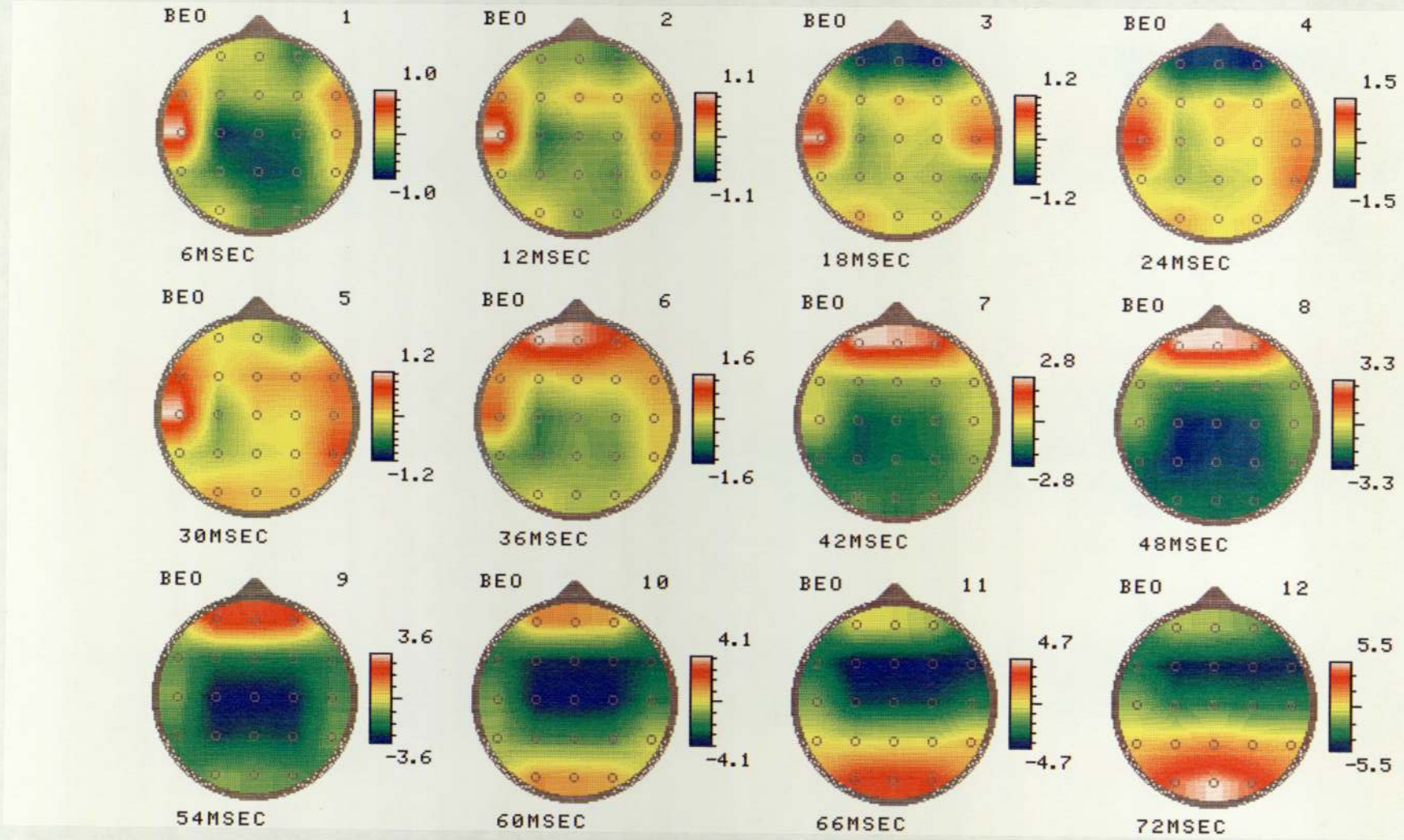

REO 1
0.9
-0.9
6MSEC
REO 2
0.8
-0.8
12MSEC
REO 3
1.2
-1.2
18MSEC
REO 4
1.3
-1.3
24MSEC
REO 5
0.9
-0.9
30MSEC
REO 6
1.2
-1.2
36MSEC
REO 7
1.8
-1.8
42MSEC
REO 8
2.2
-2.2
48MSEC
REO 9
2.5
-2.5
54MSEC
REO 10
2.7
-2.7
60MSEC
REO 11
3.3
-3.3
66MSEC
REO 12
3.6
-3.6
72MSEC

Figure 6.7:- Maps at 6 msec intervals of the group averaged data to binocular stimulation.
N.B. Each map has its own individual scale for amplitude.


BEO 1
1.0
-1.0
6MSEC
BEO 2
1.1
-1.1
12MSEC
BEO 3
1.2
-1.2
18MSEC
BEO 4
1.5
-1.5
24MSEC
BEO 5
1.2
-1.2
30MSEC
BEO 6
1.6
-1.6
36MSEC
BEO 7
2.8
-2.8
42MSEC
BEO 8
3.3
-3.3
48MSEC
BEO 9
3.6
-3.6
54MSEC
BEO 10
4.1
-4.1
60MSEC
BEO 11
4.7
-4.7
66MSEC
BEO 12
5.5
-5.5
72MSEC

6.3.0. The Effect of the BNCR on the Recording of the Frontal N75 and N120 Components of the Flash VER.

6.3.1 Method

To investigate the role of the BNCR in the recording of the frontal negatives two experiments were performed. The Biologic Brain Mapping System was used to record and map the response from 2 subjects to binocular flash stimulation with all electrodes referred firstly to a BNCR, and then to a chin reference, as well as from 2 subjects with the response referred firstly to a BNCR, and then to a linked earlobe reference. The recording parameters and set up were as described in Chapter 5, section 5.2.0.

To ensure that the frontal negative components were not a reflection of a spread of positive potential from the occipital region to the sterno-clavicular electrode of the BNCR, the following experiment was performed. A normal subject, 30 years of age, had a chain of five electrodes spaced at equal distances i.e. a 25% chain, running from the Inion to CV7, the position of the posterior electrode of the BNCR. Electrodes were also placed on the right sterno-clavicular notch, at Fz and on the left earlobe. Recordings were made from the chain of electrodes down the neck to binocular flash stimulation, referred to the earlobe. Recordings were made to flash stimulation from the earlobe electrode referred to the BNCR, from the earlobe electrode referred to Fz and from the Fz electrode referred to the BNCR. The high and low pass filters were set at 0.3 and 30 Hz respectively, stimulation was provided by a Grass PS22 photostimulator flashing at 1.1 Hz, at intensity 2 and the skin electrode resistance was reduced below 5 kΩ. An average of 50 repetitions was recorded on the Nicolet Pathfinder II.

6.3.2. Results

The recordings made to a chin or a linked earlobe reference were very similar to the responses recorded when a BNCR was used. The latency and morpholgy of the responses were comparable, especially for the ear reference (Figure 6.8 & Figure 6.9). ECG contamination and myogenic activity were a problem when using a chin reference.

The responses recorded from a chain of electrodes running from the inion to CV7, all referred to an earlobe reference, are shown in Figure 6.10. A clear P2 component is recorded from the electrode placed over the inion. It has a latency of 116 msec and an amplitude of 9.61 μV. The amplitude of this component reduced as the position of the recording electrode moved further away from the occipital region, with no identifable or consistent component being present on the trace from the electrode placed on CV7. Thus it would appear that there is no spread of the positive P2 component onto the posterior electrode of the BNCR.

The traces of the responses recorded from the earlobe electrode referred to the BNCR, the earlobe electrode referred to Fz and the Fz electrode referred to the BNCR are shown in Figure 6.11. No components can be identified on the earlobe electrode referred to the BNCR trace. The earlobe electrode referred to Fz trace shows a positive component at115 msec, with an amplitude of 8.74 μV, whilst the Fz electrode referred to the BNCR trace shows a negative component with a latency of 117 msec, with an amplitude of 10.39 μV.

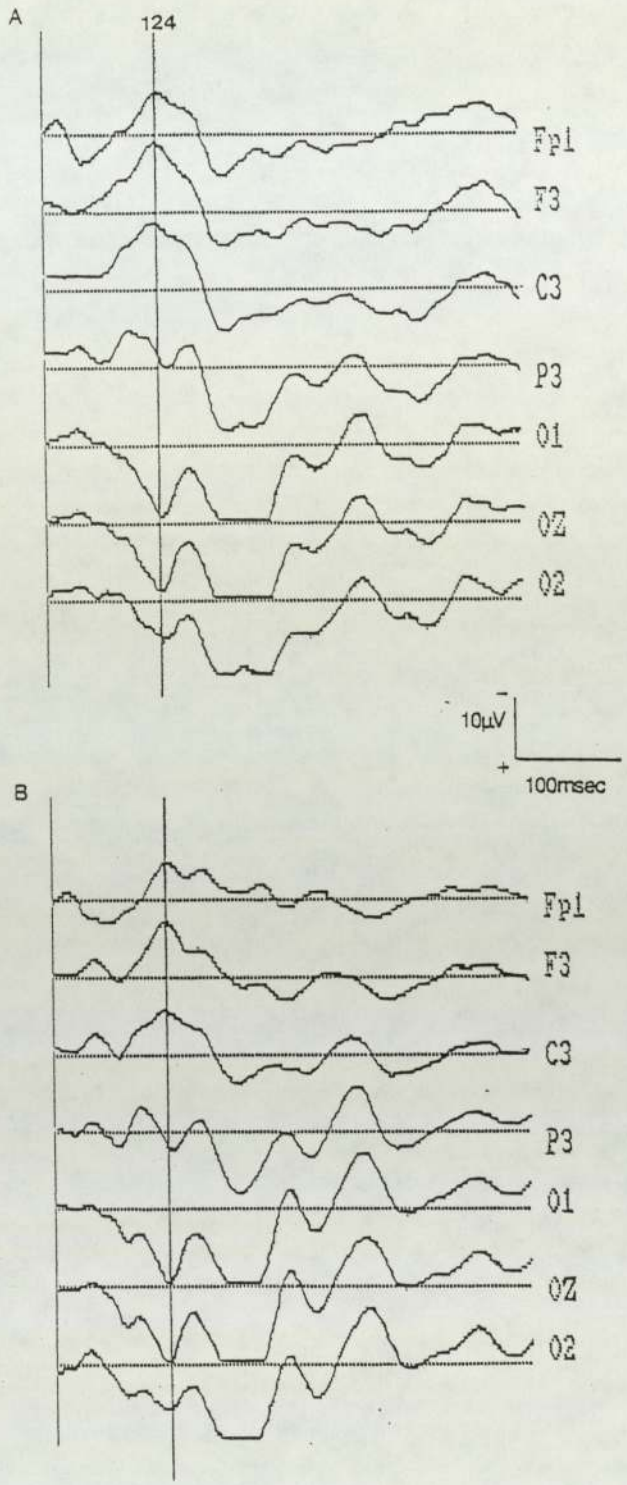


Figure 6.8:- A) Flash VER recorded from an individual to binocular stimulation referred to a BNCR. B) Flash VER recorded from the same individual to binocular stimulation referred to a linked ear reference.

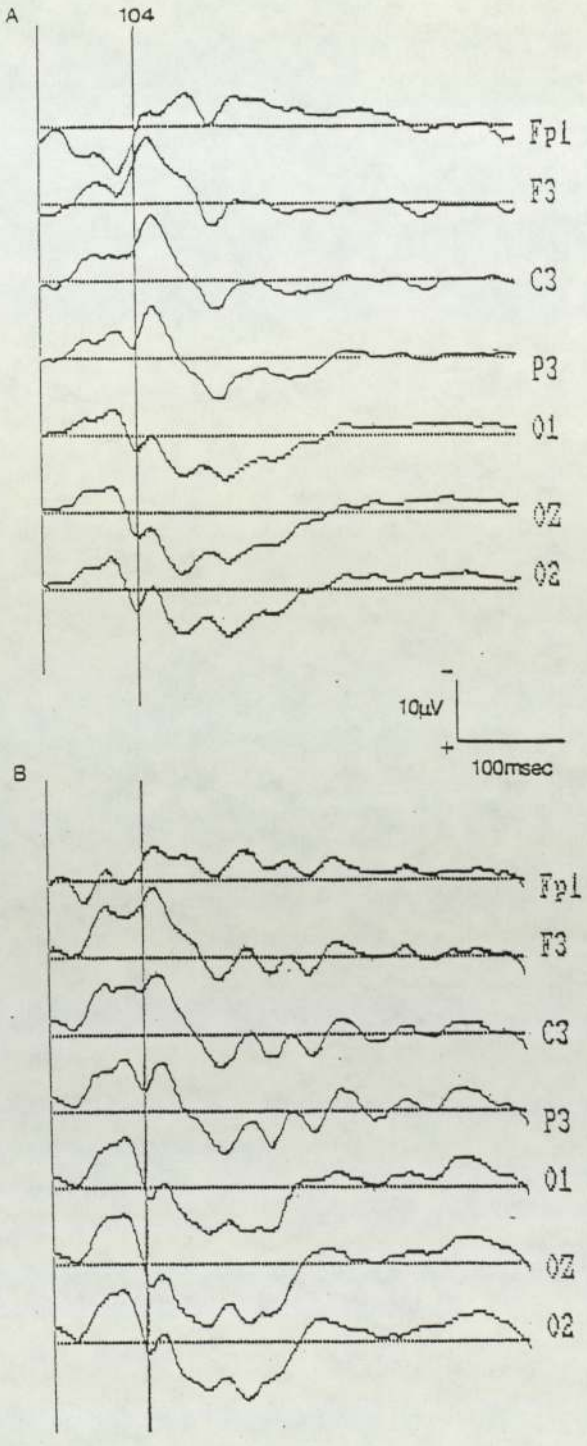


Figure 6.9:- A) Flash VER recorded from an individual to binocular stimulation referred to a BNCR. B) Flash VER recorded from the same individual to binocular stimulation referred to a chin reference.

Figure 6.10:- Flash VER recorded from a chain of electrodes running from the inion to CV7 all referred to the ear. Repeat traces are shown.

LATENCY (MSEC)		AMPLITUDE (μV)	
N1	86.00	N1-P1	9.61
N2	82.00	N2-P2	6.13
N3	81.00	N3-P3	3.47
N4	81.00	N4-P4	2.09
P1	116.00		
P2	115.00		
P3	114.00		
P4	114.00		

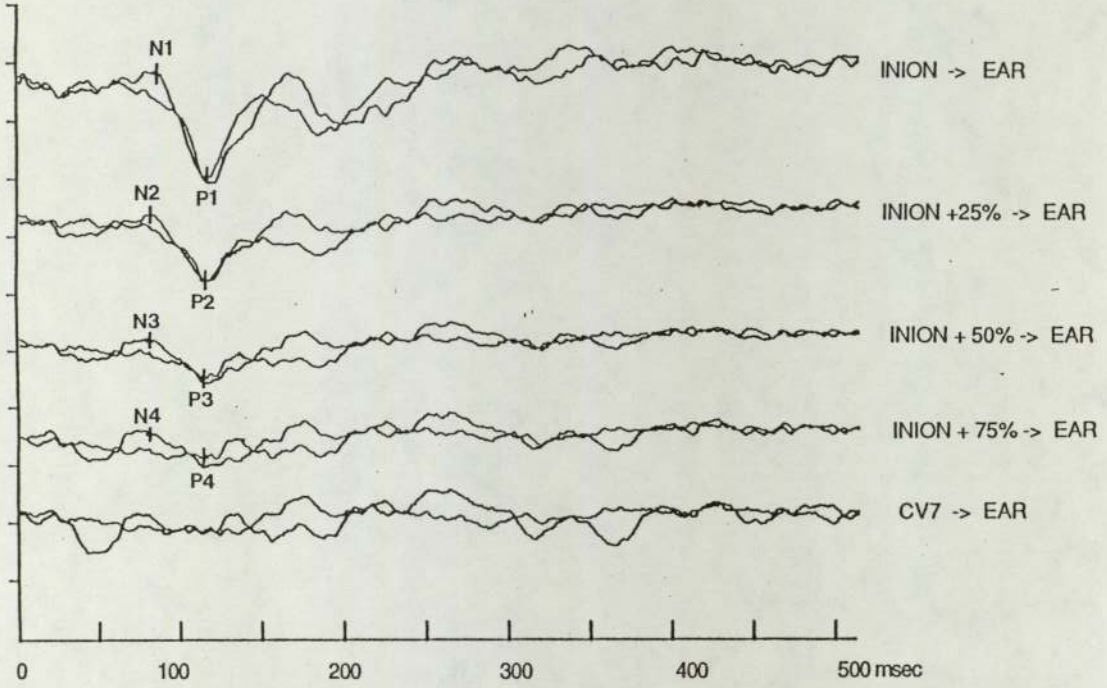
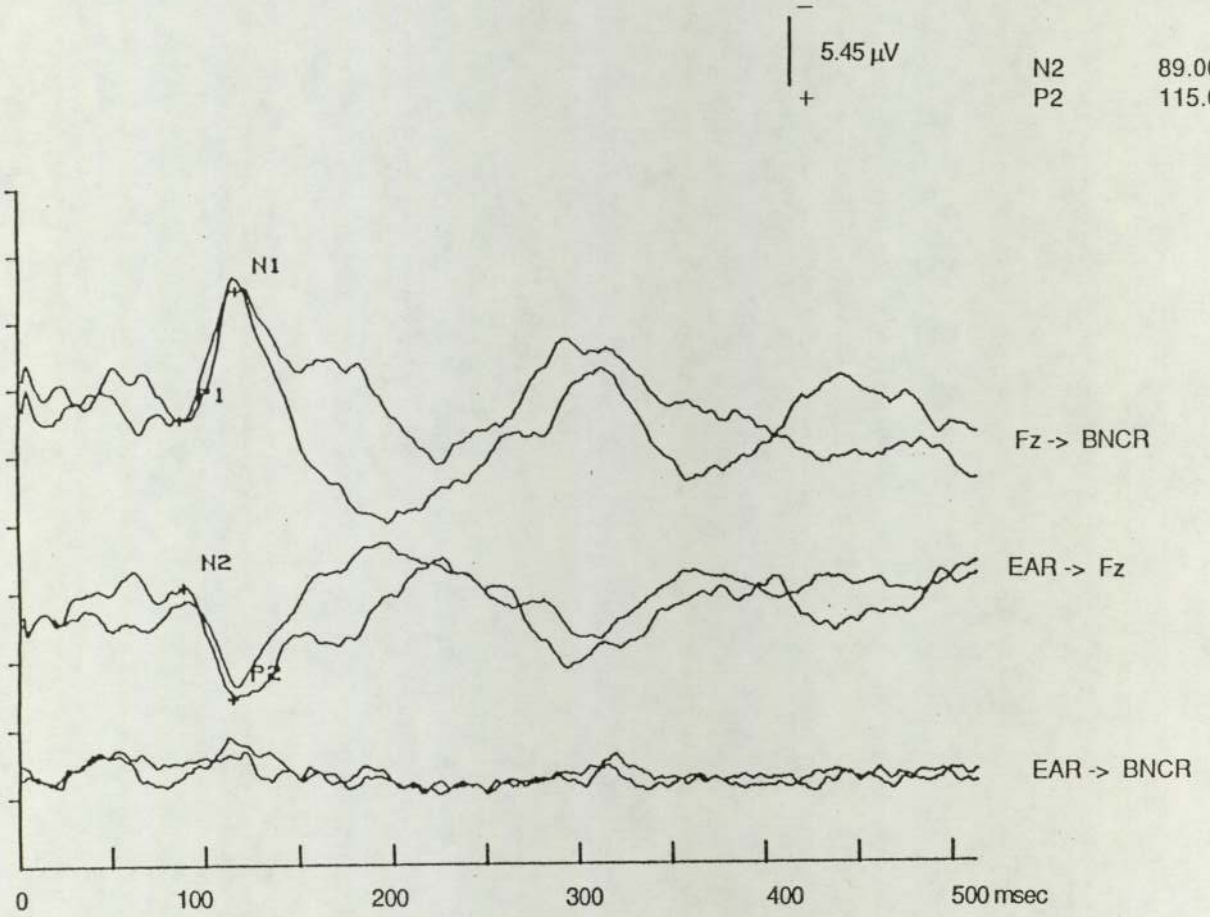


Figure 6.11:- Flash VERs to binocular stimulation :- recorded from Fz referred to a BNCR, recorded from the ear referred to Fz reference and from the ear referred to a BNCR. Repeat traces are shown.

LATENCY (MSEC)		AMPLITUDE (μV)	
P1	87.00	N1-P1	10.39
N1	117.00		
N2	89.00	N2-P2	8.74
P2	115.00		



6.4.0. Pattern Reversal and Pattern Onset / Offset Stimulation.

6.4.1 Method

The responses of the subjects in the old age group to pattern reversal and pattern onset/offset stimulation were recorded. The recording parameters and set up were as for the study in Chapter 5, section 5.2.0. A black and white 36' checkerboard pattern was presented on a Panasonic IC 30G colour monitor. The subjects were asked to fixate a red spot in the middle of the screen. The monitor screen which measured 55mm by 40mm, was held 33 cms from the subject, thus subtending a 9° 24' field of view. The contrast of the checkerboard pattern was calculated from Michelson's equation i.e. (Lmax-Lmin / Lmax+Lmin)X100 and the mean screen luminance from the equation Lmax+Lmin/2, where L=luminance. The contrast of the checkerboard pattern used in this study was 71.8% and the mean screen luminance was 81.5 candelas/m^2. The high and low pass filters were set at 0.3 and 30 Hz respectively, the pattern reversal rate and the pattern onset/offset rate was 1.1 Hz and an average of 64 repetitions was recorded. When required subjects wore a near optical correction to ensure that the pattern was clearly in focus.

6.4.2 Results

The group averaged data for the old age group to pattern reversal stimulation is shown in Figure 6.12. A clear positive component is seen over the occipital region at a latency of 106.63 msec (± 8.69), with an amplitude of 6.06 μV (± 4.32). A negative component is recorded from the frontal channels, the mean latency of which is 101.17 msec (± 7.55), with an amplitude of 3.10 μV (± 2.33). There is only a single negative component on the frontal channels, with no earlier negative components present.

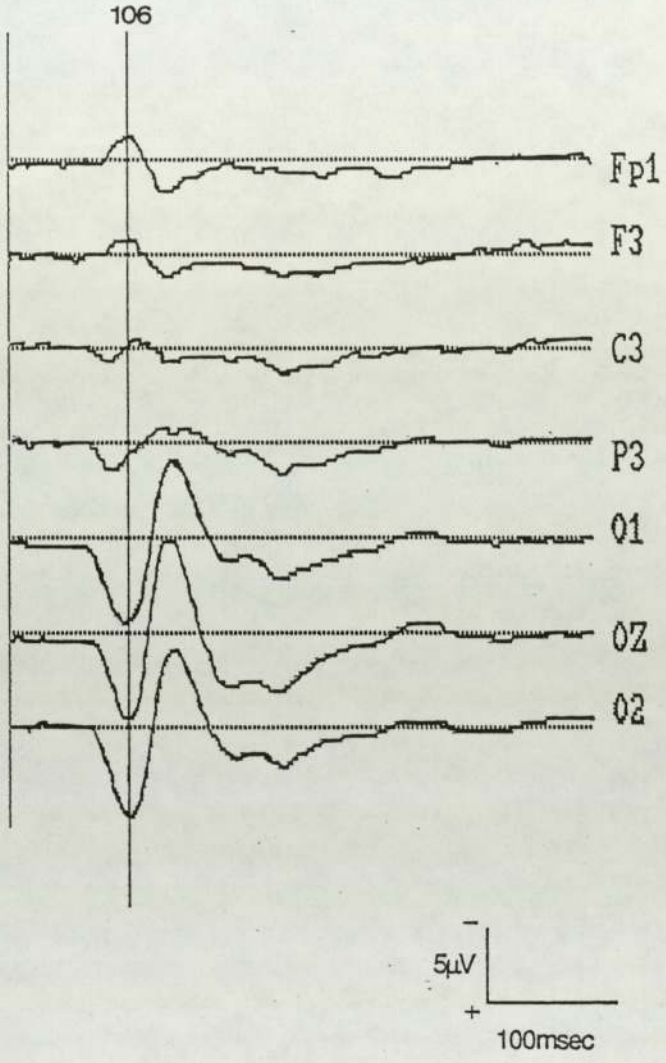


Figure 6.12:- Group averaged traces for the older age group to pattern reversal stimulation. The P100 component has a latency of 106 msec.

The group averaged data for the older group, to onset/offset pattern stimulation, is shown in Figure 6.13. Components CI and CII are clearly present over the occipital region with a latency of 90.00 msec (± 4.21) and 124.90 msec (± 5.60) respectively. The amplitudes of these components are 8.04 μV (± 6.09) and 17.38 μV (± 12.60). Frontally there is a negative component at around the same latency as the occipital positive CI component and a positive component at around the same latency as the occipital negative CII component. The latency of the frontal negative component is 94.46 msec (± 5.43) and 130.89 msec (± 5.19) for the positive component, with an amplitude of 4.07 μV (±1.46) and 9.29 μV (±5.27) respectively.

The brain maps of the group averaged data in figures 6.12 and 6.13 are shown in figure 6.14. It is interesting to note the difference in scalp topography of the P100 component of the pattern reversal response and the CI component of the onset/offset response. The P100 component is evenly distributed across the occipital region, whereas the positive CI component shows two loci of activity over electrodes O2 and O1 with a reduction in amplitude of activity over Oz, the occipital pole. There is considerable debate in the literature as to the origin of the components of pattern evoked responses. The general consensus of opinion is that the P100 component of the pattern reversal response is of striate origin (Blumhardt & Halliday 1979, Barret et al 1976, Maier et al 1987) however some authors suggest an extrastriate origin (Lehman et al 1982). Opinion as to the origin of the CI component of the onset/offset response is also divided. Again there are two schools of thought, one that it is of striate origin (Jeffreys & Axford 1972, Darcey et al 1980) and the other that it is of extrastriate origin (Lesevre & Joseph 1979, Maier et al 1987).

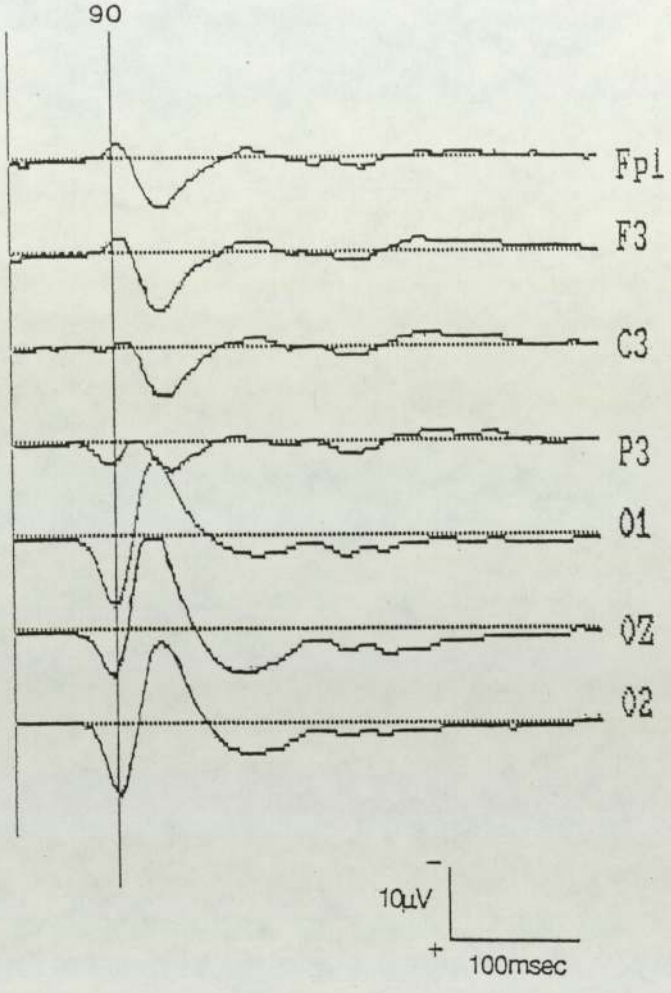


Figure 6.13:- Group averaged traces for the older age group to pattern onset/offset stimulation. The CI component has a latency of 90 msec.

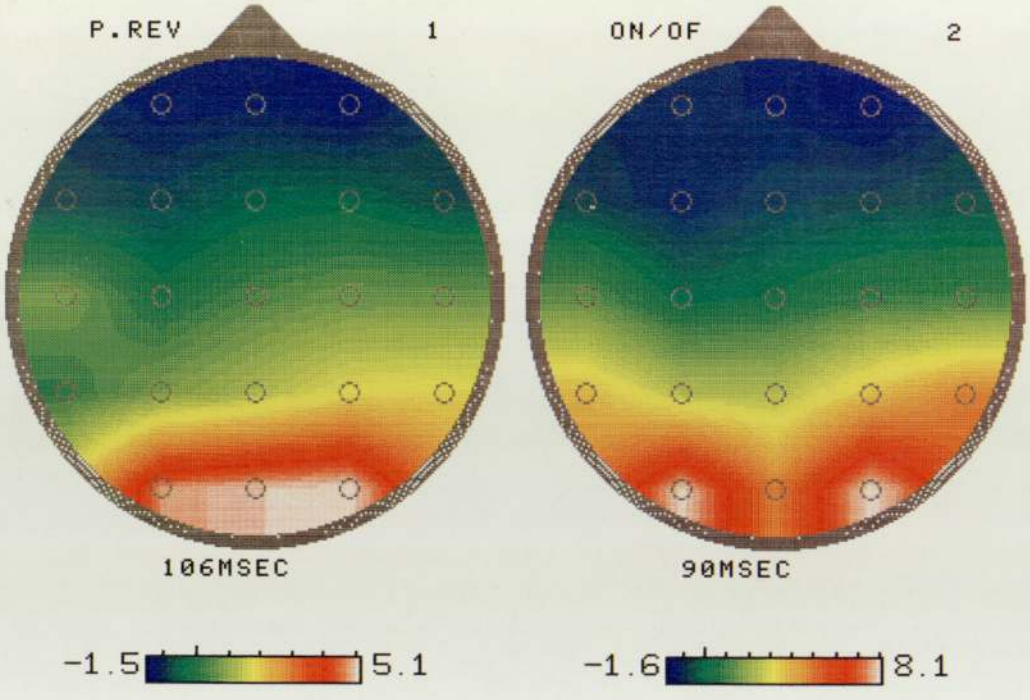


Figure 6.14:- Brain maps of the group averaged 1) pattern reversal and 2) pattern onset/offset data, shown in figures 6.12 and 6.13. The pattern reversal map is at 106 msec, the latency of the P100 component, and the pattern onset/offset map is at 90 msec, the latency of the CI component.

6.5.0. DISCUSSION

The results presented above would strongly suggest that the frontal negative components recorded during flash stimulation are not due to volume conduction of the ERG, are not due to potential spread onto the balanced non-cephalic reference from the occipital region and are not solely related to the age of the subject.

If the frontal N75 or N120 components of the flash VER had been of ERG origin, with monocular stimulation one would have expected the response to be asymmetrical, with the greater amplitude of response being on the side of stimulation. As was shown the ERG responses was asymmetric, being present over the right eye. However, the N75 and N120 components were bilateral and their development was independant of the ERG. In addition, if the N75 component had been part of a volume conducted ERG one would have expected it to be recordable in all three age groups, with its greatest amplitude being recorded in the young age group, the age group in which the ERG has the largest amplitude (Peterson 1968, Wright et al 1985).

The ERGs latencies recorded in this study were of around the normative values given by other workers, although direct comparisons are difficult to make as a recognised ERG set up was not used. Subjects were not dark adapted, and as white light was used, the response recorded was likely to be a mixed rod and cone response.

The frontal negative components recorded to flash stimulation are not the result of using a balanced non-cephalic reference. Firstly, very similar responses were recorded when the reference site used was either the chin or linked earlobes. Secondly, it was shown that the BNCR was a quiet reference for the recording of the flash VER, with no element of potentials recorded from over the occipital region spreading down to region of CV7. This agrees with the work of Lehtonen & Koivikko (1971). As previously stated the P1

component is smaller or of equal amplitude to the P2 component (Harding 1982). As there was no spread of the P2 potential, the same rationale should apply to a P1 component. If the frontal negative components were as a result of positive potential spread onto the CV7 electrode, then a frontal negative component would not be recorded without the presence of an occipital positive component. The results in the previous Chapter have shown that this is not the case and that a negative N75 component can be recorded in the absence of a P1 component.

The response recorded from the Fz electrode, referred to the BNCR, showed a negative component at 117 msec which was very similar to the latency of the positive component recorded on the occipital channels (116 msec)(Figure 6.11), thus confirming the earlier findings. Earlobe recordings referred to a BNCR, produced no detectable response. This would suggest that the earlobe is a relatively quiet reference site for the recording of the flash VER. The use of single or linked mastoids as a quiet reference site for the recording of the pattern reversal VERs has been suggested by Spitz et al (1986) and Shih et al (1988).

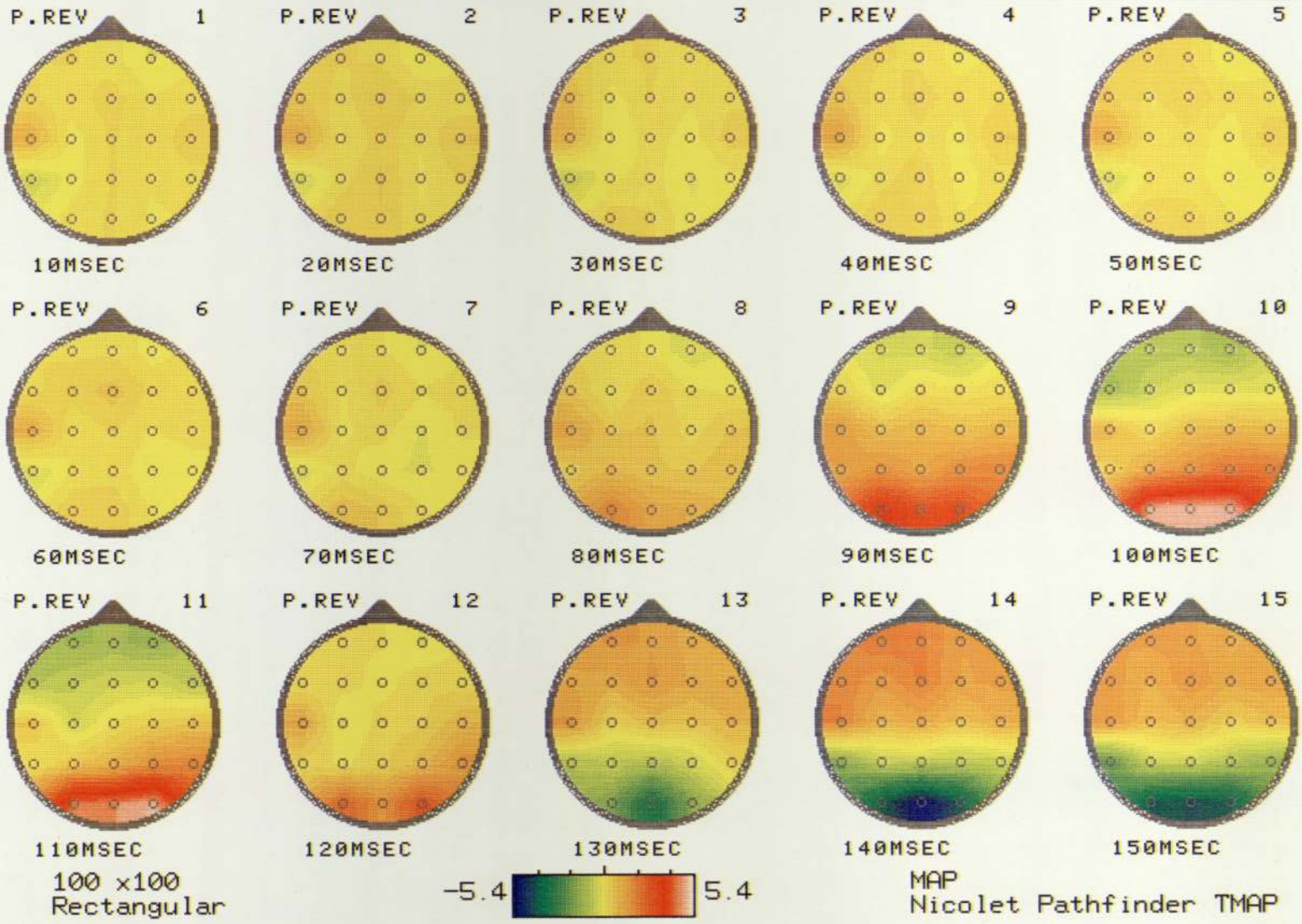
When the earlobe was referred to a Fz reference, a positive component was recorded at 115 msec, with an amplitude of 8.74 μV (Figure 6.11). As no response was recorded when the ear was referred to a BNCR, perhaps this positive component reflects the negative activity on the Fz reference.

The onset/offset stimulation showed that over the frontal region a component was recordable with the opposite polarity to the components recorded over the posterior channels at around the same latency. The use of pattern reversal stimulation confirmed the finding of other workers (Asselman et al 1975, Spitz et al 1986, Shih et al 1988) in that the frontal channels are not inactive, but show negative activity at around the same latency as the occipital positive component. The results of these studies, although

using different check sizes (23' and 52'), confirmed the presence of a frontal negative component at around the same latency of the P100 component. The check size used for this experiment (36') was limited by the desire to have the screen at 33 cms, the optimum working distance for the majority of reading spectacles. The size of the monitor was determined by the need for a hand held monitor as the subjects were in a supine position. However, the check size used in this study was between the sizes used in previous studies with comparable results. Age studies have shown there is very little change in the morphology of waveform of the pattern reversal response across the age range and that from the age of about twenty years, there is very little change in the waveform of the onset/offset response (Wright et al 1985). It is clear with a patterned stimulus that there is no appearance of additional components with age, either occipitally or frontally. Therefore this would suggest that the frontal negative N75 component recorded to flash stimulation is related to the type of stimulation and is not purely a function of the age of the subject.

Examination of the group averaged pattern reversal data, at 10 msec intervals, shows there is very little activity prior to 80 msec. An occipital positive P100 potential starts to develop between 80 and 90 msec and reaches a maximum between 100 and 110 msec. Over the same time period a negative potential develops over the frontal region (Figure 6.15). After 110 msec the occipital positive and frontal negative potentials reduce in amplitude and by 130 msec the following occipital negative potential has started to develop.

Figure 6.15:- The group averaged data of the older group to pattern reversal stimulation mapped at 10 msec intervals.


P.REV 1
10MSEC
P.REV 2
20MSEC
P.REV 3
30MSEC
P.REV 4
40MESC
P.REV 5
50MSEC
P.REV 6
60MSEC
P.REV 7
70MSEC
P.REV 8
80MSEC
P.REV 9
90MSEC
P.REV 10
100MSEC
P.REV 11
110MSEC
P.REV 12
120MSEC
P.REV 13
130MSEC
P.REV 14
140MSEC
P.REV 15
150MSEC
100 x100
Rectangular
-5.4
5.4
MAP
Nicolet Pathfinder TMAP

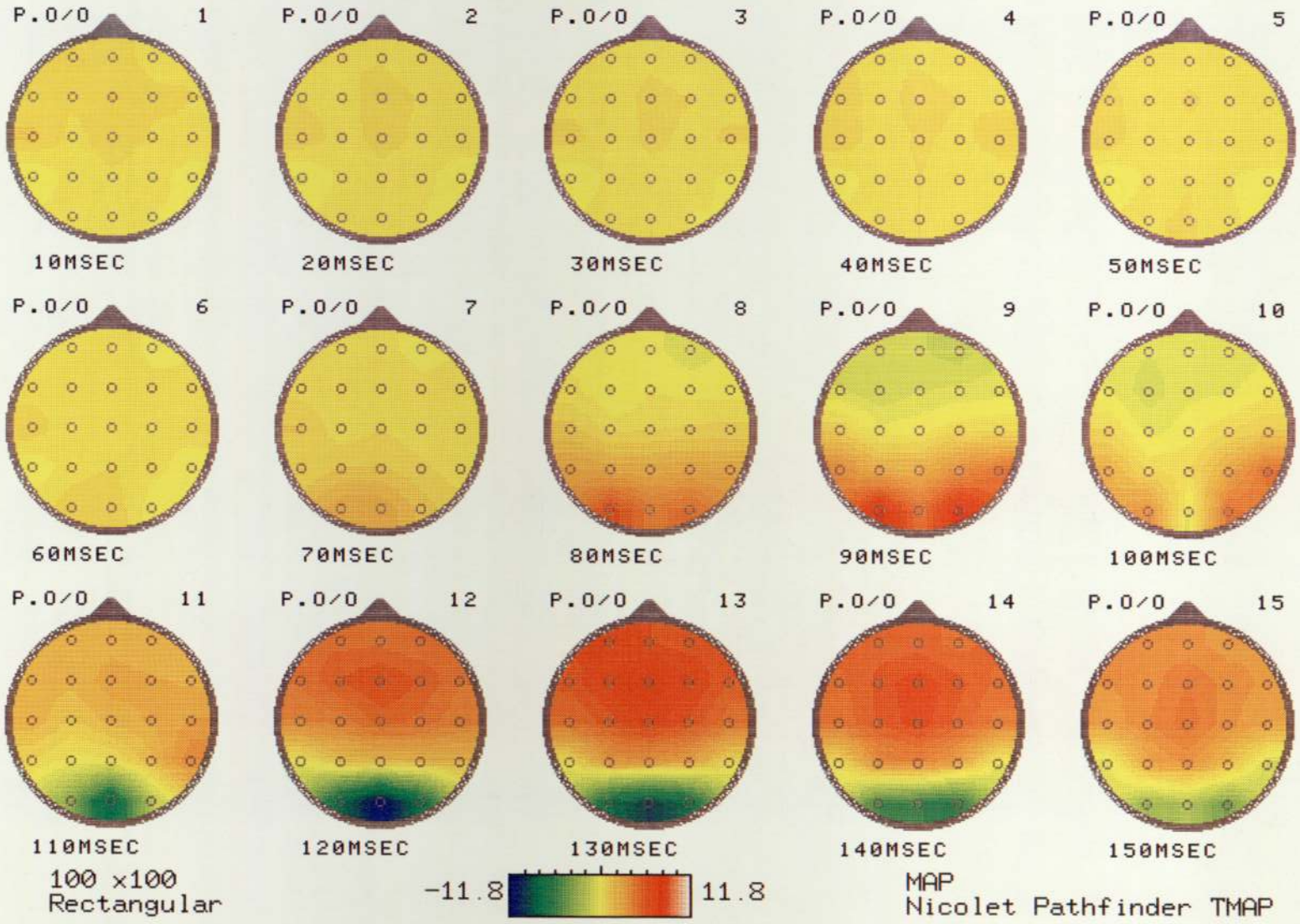
The pattern onset/offset response, presented in the same way, shows there is very little activity prior to 70 msec. A typical occipital CI response then develops reaching its maximum at about 90 msec. A small amplitude frontal negative potential over the electrodes Fp1 and Fp2 is seen to develop over the same time period (Figure 6.16). A reduction in these potentials then occurs and by 110 msec the occipital negative CII component and a frontal positive potential have started to develop.

As regards topography, the scalp distribution of the positive P100 component of the pattern reversal VER is very similar to the distribution of the positive P2 component of the flash VER being spread symmetrically across the occipital region of the head. Although there are similarities in the scalp distribution of the positive P2 component of the flash VER and the P100 component of the pattern reversal VER, the topography of the associated negative components differ. The negative component of the pattern reversal VER has a more anterior distribution than the negative components of the flash response.

The CI component of the pattern onset/offest response has a different scalp distribution to the other components, with separate loci of activity over the two hemispheres with a reduction in amplitude over the occipital pole.

The similarity in scalp topography between the P2 and P100 components is interesting as various workers have postulated that the P2 component is extrastriate in origin whereas the P100 component of the pattern reversal response is thought to be striate in origin (Wright et al 1987, Maier et al 1987).

Figure 6.16:- The group averaged data of the older age group to pattern onset/offset stimulation mapped at 10 msec intervals.


P.0/0 1
10MSEC
P.0/0 2
20MSEC
P.0/0 3
30MSEC
P.0/0 4
40MSEC
P.0/0 5
50MSEC
P.0/0 6
60MSEC
P.0/0 7
70MSEC
P.0/0 8
80MSEC
P.0/0 9
90MSEC
P.0/0 10
100MSEC
P.0/0 11
110MSEC
P.0/0 12
120MSEC
P.0/0 13
130MSEC
P.0/0 14
140MSEC
P.0/0 15
150MSEC
100 x100
Rectangular
-11.8
11.8
MAP
Nicolet Pathfinder TMAP

6.6.0. SUMMARY

The frontal negative components recorded during a flash visual evoked response are not the result of ERG contamination, the use of a BNCR and are not a general visual response as a function of the age but are related to flash stimulation.

The scalp topography of the occipital P2 component resembled that of the P100 component of the pattern reversal response rather than that of the CI component of the pattern onset/offset response.

CHAPTER 7

DISCUSSION

7.1.0. SUMMARY OF RESULTS

The major findings of this study are given in summary below:-

1) The eye closure study has shown that when recording a flash VER through a closed eyelid the latency of the P2 component increases whilst the latency of the P1 component does not. The results would suggest that the increase in latency of the P2 component was not the result of a luminance effect, the eyelid diffusing the light, or an increase in background alpha activity, but maybe the result of the eyelid acting as a red filter. The differing behaviour of the P1 and P2 components when recorded through closed eyelids would suggest that they have different cortical generators.

2) The recording of the flash VER from subjects of various ages has shown the effects of age on the components of the flash VER. The P2 component of the flash VER could be recorded from subjects of all ages and its latency increased with the age of the subject. The incidence of a recordable P1 component was found to increase with age. The amplitude of the P1 component, but not the latency, also increased with age.

3) The topographic study showed that during the recording of a flash VER the frontal channels showed negative activity, the morphology of which altered with the age of the subject. A frontal negative potential was recorded in subjects of all ages, at around the same latency as the P2 component. In the middle and old age groups an additional earlier frontal negative component was found to develop at around 50 msec, with a maximum amplitude at around 75 msec. An occipital P1 component was recordable in

the old age group at around 75 msec, peaking at the same latency as the N75 component. Although there was a comparable frontal negative (N75) component in the middle age group, there was no comparable P1 component over the occipital region. The young age group did not show a comparable frontal negative (N75) or occipital positive (P1) component.

The scalp distribution of the occipital positive P1 and P2 components of the flash VER were found to differ. The P1 component was recordable over the parietal region, as well as the occipital region, whereas the P2 component was confined more to the occipital region. The scalp distribution of the occipital P2 component was very similar to that of the occipital P100 component of the pattern reversal response and quite unlike the scalp distribution of the occipital CI component of the pattern onset/offset response. Although the positive occipital potential distribution of the P2 and P100 components were similar, the distribution of their frontal negative components was different. The negative potential associated with the P2 component was recordable over the frontal and central regions, whereas as the frontal negative recorded at the same latency as the P100 component was recorded principally over the frontal region with very little central involvement.

4) The results of the topographic study illustrated some of the pitfalls of the choice of Fz as a reference site for the recording of a flash visual evoked response. The changing morphology of the negative activity over the frontal region will influence the amplitude and latency of the positive components recorded over the occipital region if the reference electrode is placed in the frontal region.

7.2.0. DISCUSSION OF RESULTS

It may be concluded from both the literature and the results recorded in this thesis that the cortical generators of the P1 and P2 components of the flash VER are different. This conclusion is based on their behavioural differences. The P2 component can be recorded throughout life, whilst the incidence of recording a P1 component increases as the age of the subject increases. As the age of the subject increases the latency of the P2 component increases, with no accompanying increase in the latency of the P1 component. When a flash VER is recorded through a closed eyelid the latency of the P2 component increases whereas the latency of the P1 component remains unaffected. Finally, in Alzheimer's disease the latency of the P2 component increases whilst that of the P1 component remains the same.

If the cortical generators of the two components are different, are they within the same cortical region? Are they confined to the striate cortex i.e. two generators in area 17 or do they lie within different regions of the cortex e.g. one generator in one or more of areas 17, 18 and 19? If part of the response is generated from area 18 or 19, is the route of transmission of the evoking signal from the eye via the lateral geniculate body and area 17 or via the superior colliculus to area 18.

The results from intracerebral recordings in humans and monkeys provides useful information that cannot be obtained from scalp recording. Mitzdorf & Singer (1979) showed that the afferents from the magnocellular layers of the LGB synapsed in layer IVcα of area 17 and those from the parvocellular layers synapse in layer IVcβ of area 17, subsequently projecting to layer IV of area 18. Analysis by current source density showed that early sinks were the result of monosynaptic activity whereas later sinks were mediated by polysynaptic activity. Kraut et al (1985) also found that the parvocellular afferents synapse in layer IVcβ of area 17. As they found a large source in lamina IVcβ during the 60-110 msec after flash stimulation, they concluded that the flash VER

results from stimulation of the parvocellular cells of the LGB. As the thalamic cortical input does not last beyond 60 msec, it would appear that the components of the flash VER are the result of monosynaptic and polysynaptic mediated cortical activity. The above findings would suggest that the P2 component is the result of polysynaptic activity, whilst the P1 component is an oligosynaptically mediated event.

Alteration of the flash VER by experimental means or as a result of a pathological process (including aging) results in an increase in the latency of the P2 component, whilst the latency of the P1 component is unchanged. One possible explanation is the disruption of synaptic activity e.g. the increase in latency of the P2 component with age may be the result of a reduction in synaptic efficiency. Alzheimer's disease is associated with a reduction in the transmitter substance acetylcholine, causing defects in synaptic transmission. The fewer synapses involved in the transmission of a component the less likely its latency is to be delayed by such processes i.e. the P1 component compared to the P2 component.

The topographic study has shown the scalp distribution of the P1 and P2 components to be different. Both components have a similar spread of positive potential across the occipital region, with a frontal region of negative potential. The positive potential of the P2 component is confined to the occipital area, whereas the positive potential of the P1 component is also present over the parietal region. The positive potential of both components is evenly distributed across the occipital region without particular localisation of activity. Ducati et al (1988) by the use of intracerebral recordings in humans, showed that the generator of the P1 component was more superficial in the cortex than the generator of the P2 component. This may explain the wider scalp topography of the P1 component. It is possible that the N120 component may represent the opposite end of a dipole which generates the P2 component of the flash VER. The frontal negative potential (N120) develops at about the same latency as the P2 component and increases in latency with age, as indeed does the P2 component. The frontal negative N75 component, however, develops earlier than the P1

component, not only during the response, but with age. This may indicate that the N75 component does not represent the opposite end of a dipole generating the P1 component.

Examination of the topography of the response recorded at scalp level does not enable the exact location of the cortical generators of the response to be identified. Hoeppner et al (1984) looked at subjects after complete occipital lobectomies and found a normal response over the ablated side and a distorted signal over the intact hemisphere. This suggests conclusions based entirely on the scalp topography may be misleading. This is borne out with the paradoxical lateralisation of responses recorded to half field pattern reversal stimulation, the maximum response being recorded over the ipsilateral hemisphere rather than the anatomically correct contralateral hemisphere. These responses result from generators of a pattern reversal response, which, although situated in the contralateral hemisphere, are orientated towards the ipsilateral hemisphere and thus result in a larger response over that hemisphere (Barrett et al 1976).

Positron emission tomography has been used to investigate which areas of cortex are activated by stimulating the visual system with a flash of light. One study reported that most of the activity was in area 17, with some involvement of areas 18 and 19 (Phelps et al 1981), whilst an other found that areas 17, 18 and 19 were equally affected (Celesia et al 1982). Celesia et al (1982) thought that the topography of the response observed by recording from electrodes placed on the scalp is the result of interactions between all three cortical areas, rather than sole volume conduction of striate dipoles. This hypothesis is supported by the work on cortical blindness, which shows that a normal pattern and flash VER can be recorded from area 17 alone, or areas 18 and 19 alone, in patients with no visual perception. It would therefore seem that all three cortical regions are involved in the generation of the flash VER.

The route of transmission of the evoking signal is believed to be either via the LGB to the cortex or via the superior colliculus to the cortex or a combination of the two. Anatomical studies show that only 10% of fibres from the retina pass via a non-geniculate pathway to the cortex and none of these project from cells of the P-beta or X-cell type, i.e. the type of cell which projects to the parvocellular layers of the LGB, the type of cell afferent thought to produce a flash VER (Kraut et al 1985). The pathway of some nerve fibres from the eye to the cortex is via the superior colliculus, but the function of the pathways remains ill defined.

The appearance of a P1 component with age, could be the result of a new event or the removal of a factor which previously masked or inhibited the P1 component. Wright et al (1985) suggested that the P1 component is not recorded in the young as it is swamped by the larger amplitude P2 component. As the subject ages, the latency of the P2 component increases, thus revealing a P1 component. One of the findings from this study would not support this argument. With eye closure the latency of the P2 component in the young age group increased without the appearance of a P1 component. The use of a red filter also increased the latency of the P2 component without the emergence of a P1 component. If the P1 component is the result of a new event, the increase in latency of the P2 component would have no effect on its emergence.

The study suggests the use of the P2 component as the most reliable component of the flash VER upon which to base normative data. However, the changing morphology of the negative activity on the frontal channels should be taken into account when Fz is chosen as a reference site for the recording of the flash VER. The frontal negative activity (N120) and the occipital positive P2 component of the flash VER are of about the same latency throughout the age range and therefore the use of a midfrontal reference would generally result in an enhancement of the P2 component of the response.

However, in cases where the two are not synchronous the use of a midfrontal reference would result in an apparent latency shift of the P2 component. The choice of a midfrontal reference site in subjects in the middle age range may result in the artificial appearance of a P1 component, which in fact is a reflection of the frontal negative N75 component. As the subjects increase in age the use of a midfrontal reference would result in the enhancement of the P1 component. If the two components are not synchronous an apparent latency shift may result.

The choice of the central electrodes, C3 and C4, as reference sites for the recording of a flash VER would have similar limitations, although the negative activity over this region is of slightly smaller amplitude. A balanced non-cephalic reference would appear to be the reference of choice. If an Fz reference is used the results obtained should be viewed in the light of the negative activity in the frontal region.

The use of the balanced non-cephalic reference for the recording of a pattern reversal response has shown that the frontal channels rather than being inactive show negative activity. Although the morphology of the negative activity appears not to change with age, the choice of the frontal region as a reference site for the recording of the pattern reversal VER will have an affect on the occipital P100 component recorded. If the frontal negative and occipital positive are synchronous then use of a frontal reference will enhance the P100 component. If they are asynchronous the result will be an apparent shift in latency combined with an enhancement of the P100 component. Although there is negative activity over the central region, it is of smaller amplitude and if a non-cephalic reference is not feasible, a central reference would have less effect on the occipital P100 component recorded.

7.3.0. THE ADVANTAGES AND DISADVANTAGES OF BRAIN MAPPING EVOKED POTENTIALS.

The aim of mapping systems is to ease the interpretation of the recorded data for the observer. An iso-potential map, drawn over an outline of the head, is easier to assimilate for both the experienced and inexperienced observer than the simultaneous viewing of 21 traces. The use of either a colour or grey scale makes the detection of areas of negative and positive activity relatively simple. The more recent brain mapping packages allow for the creation of normative data bases and include softwear for statistical analysis of data.

A disadvantage of brain mapping is that the information it provides may be misleading in certain circumstances. A brain map represents the evoked response at a moment in time with no information being given as to events prior to or after that moment in time. Evoked responses have both a temporal and a spatial dimension and viewing the traces enables an assessment of these variables to be made, whereas this information is lost from an isolated brain map. An example of this was discussed in Chapter 5, p140, when it appeared that a frontal positive component was present in the middle age group, at around 90 msec. This was an artefact resulting from baseline drift and would have been ignored if the traces had been viewed by eye.

It is possible to highlight, depending on the colour scale used, certain aspects of the data and give them an apparent importance not evident from viewing the traces. Using a 32 colour scale to cover a small voltage range can be a hindrance, as insignificant differences in voltage across the traces will map as different colours. The resulting map will not look homogenous but significantly asymmetrical.

The conclusion to be drawn from this study is that brain mapping of an evoked response is an aid to interpretation. However, the interpretation of a map may be misleading unless viewed in conjunction with the original traces.

7.4.0. FUTURE WORK.

The mapping of the response to flash stimulation, across the age range, using magnetoencephalography would provide information as to the depth of the generators of the evoked response recorded. This would, perhaps, enable the confirmation of a shallower origin for the P1 component in the cortex compared to the P2 component and thus explain its more widespread scalp distribution.

The brain mapping of patients with senile dementia, to flash stimulation using a balanced non-cephalic reference, would provide information as to whether the increase in the latency of the P2 component was in fact an increase in latency of the occipital component, with concurrent increase in the frontal N120 component, or solely an increase in the frontal N120 component reflected onto the occipital P2 component as the result of using of an Fz reference.

As previously stated Alzheimer's disease is thought to be a disease associated with a reduction in the transmitter substance acetylcholine. If the increase in latency of the P2 component is due to a reduction in acetylcholine having an effect on synaptic transmission, treating these patients with drugs to increase acetylcholine production, or inhibit its clearance by cholinesterases, may shorten the latency of the flash response. This would support the hypothesis that the P2 component is of polysynaptic origin.

The diagnostic role of the P1 component is limited, but investigation of the loss of the P1 component in patients with chronic open angle glaucoma may show it to have a predictive or prognostic role in disease. If the P1 component is absent from the response recorded from eyes with chronic open angle glaucoma this might reflect a

concurrent loss or absence of the N75 component. If the loss of the P1 component was confirmed in chronic open angle glaucoma it may be possible to relate this to visual field defects, thus providing information as to the areas of retina from which the fibres which generate the P1 component originate.

APPENDIX

SUPPORTING PUBLICATIONS

1) Hobley Angela and Harding Graham. (accepted in press 1988)
The effect of eye closure on the flash visual evoked response.
Clinical Vision Sciences.

2) Hobley A and Harding G. (1988)
The effect of eye closure upon the flash visual evoked response.
Presented at the Society of Experimental Optometry 1987.
Ophthamlic. & Physiol. Opt. 8: 106.

3) Hobley Angela and Harding Graham. (accepted in press 1988)
The effect of different reference sites on the incidence and amplitude of the P1 component of the falsh VER.
Presented at the EEG Society, Leeds 1988.
Electroenceph. clin. Neurophysiol.

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Clin. Vision Sci. Vol. 00, No. 0, pp. 000–000, 1988
Printed in Great Britain.

0000-0000/88 $3.00 + 0.00

RESEARCH REPORT

THE EFFECT OF EYE CLOSURE ON THE FLASH VISUALLY EVOKED RESPONSE

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Abstract—Recording the flash visual evoked response (VER) through a closed lid produces a significant increase in the latency of the major positive component (P2 occurring at about 100–120 ms) but no significant increase in the latency of the earlier positive component (P1 occuring at around 60–70 ms). The present study shows that this increase in P2 latency does not appear to be caused by a reduction in the stimulus luminance due to the closed lid or the eyelid acting as a Ganzfeld form of stimulation. The latency of the P2 component recorded through a closed lid is not altered by performing mental arithmetic during the recording, suggesting that the increase in P2 latency is not due to change in the background EEG activity. However, the placing of a red filter in front of the photostimulator with the eye open produced the increase in P2 latency which was evident on eye closure. Thus a significant factor in the increase in P2 latency on eye closure appears to be due to the eyelid acting as a red filter.

Key words—Visual evoked response; flash visual evoked response; eye closure.

INTRODUCTION

It is well recognized that the effect of eye closure upon the electroencephalogram (EEG) is an increase in alpha activity (Adrian and Matthews, 1934). The International Federation for Electroencephalography and Clinical Neurophysiology's definition of alpha rhythms is that they are "present most markedly when eyes are closed and attenuated during attention especially visual" (Storm van Leeuwen, 1966). Reports as to the effect of eye closure upon the flash visually evoked response (VER) are less numerous. An increase in the amplitude of the early response of the flash VER has been reported (Halliday, 1982). Poole and Weaving (1987) showed that on eye closure the P100 component of the flash VER had an increased latency of around 5–10 ms whereas the increase in the latencies of the earlier components was smaller.

The effect of eye closure upon the flash VER has clinical importance as for example in patients unable to open their eyes such as babies or major eye injuries, in cases of drowsiness or where responses are required during sleep.

The reported increase in the latency of the major positive component (P2 occuring at about 100–120 ms) with a smaller increase in the earlier positive component (P1 occuring at around 60–70 ms) could result either from the closed lid causing a reduction in the intensity of the stimulus: the closed lid acting as a red filter; or as a Ganzfeld form of stimulation. Alternatively eye closure could cause an increase in the background alpha activity which in turn affects the averaged VER recorded due to a change in the signal/noise relationship. Since eye closure usually increases the amplitude of the alpha rhythm and since alpha rhythm may indicate lower attention a further possibility was investigated, that the effects on the components of the VER may be related to inattentiveness.

In this paper we investigate the above factors to ascertain which, if any, mimic the result of eye closure.

METHODS

The effect of eye closure on two age groups

To assess the effect of eye closure on the P1, N2 and P2 components of the VER (Harding, 1974) two age groups were investigated. Since the P1 component is more readily identifiable as the age of the subject increases (Wright *et al.*, 1985) an older age group was required to compare the effect on both the P1 and P2 components.

The older age group consisted of 10 subjects with a mean age of 52.2 yr (range 41–63 yr). All these subjects were healthy volunteers with no ophthalmolgical or neurological disorders. Flash VERs were recorded monocularly right and left in both eye open and closed situations with the non-stimulated eye being occluded. A study of 5 normal subjects showed that there was no significant effect on the results recorded whether the occluded eye was kept open or closed under the occluder. It was not, therefore, necessary to control for the state of the occluded eye. Standard silver–silver chloride electrodes were placed on the scalp at O1 and O2 and referred to FZ. The resistance of the skin electrode interface was reduced to below 5 kΩ. Stimulation was provided by a Grass PS22 photostimulator, which had been fitted with a diffusing screen, at intensity 2 flashing at 1 Hz which is equivalent to 68 cd/m^2 per s. The photostimulator was placed 33 cm infront of the subject in all experiments. The high and low pass filters were set at 0.5 and 30 Hz respectively and the average of 50 repetitions was recorded on a Nicolet Pathfinder II. Three recordings for each eye for each stimulus condition were made. The above recording conditions were as for a routine clinical VER.

The younger age group consisted of 10 subjects, all healthy volunteers with a mean age of 22.1 yr (range 16–28 yr). Flash VERs were recorded as above.

Four further studies were performed using groups of 10 young normal subjects. To assess the effect of reduced intensity of stimulation, flash VERs were recorded with the stimulated right eye closed and then with the right eye open and four steps of neutral density filter placed in front of the photostimulator. The filter steps were from 0.00, a baseline measurement, to 3.00 log units in 1.00 log unit steps. The effect of performing mental tasks whilst recording flash VERs was investigated by recording flash VERs with the subjects either in a relaxed state or counting backwards aloud in 7's from a previously given three figure number. These conditions were imposed on both eye open and eye closed runs. To assess whether the closed lid was diffusing the light, i.e. producing a Ganzfeld effect, baseline flash VERs were recorded for eye open and eye closed situations to white light. The subject then wore a pair of wide angled goggles fitted with diffusing opal lenses with side flaps in order to produce a Ganzfeld effect and had VERs recorded when the open right eye was stimulated with either red or white light. Finally, flash VERs were recorded without the opal goggles when the right eye was stimulated in both eye open and eye closed situations to white light.

VERs were then recorded when the open eye was stimulated with either red or green luminance-matched light. To luminance match the red and green light two Medelec OS5 photostimulators were placed side by side flashing alternatively at 15 Hz and viewed through a diffusing screen. The position of one photostimulator was set and the distance of the other one from the diffusing screen was altered until minimum flicker was achieved. The red Rosco No. 26 and green Rosco No. 86 filters were placed in front of the photostimulators and viewed again at a rate of 15 Hz. Neutral density filter was placed in front of the green filter until minimum flicker was achieved. Four different observers performed the task and the same result was achieved by them all. For all the above studies the Grass PS22 photostimulator was used and maintained at intensity 2 except for the colour study when the Medelec OS5 photostimulator was used at intensity 2, the non-stimulated eye was occluded and the electrode positions and recording setting were as described above.

RESULTS

The effect of eye closure on the two age groups

The group averaged results of the effect of eye closure upon the flash VER for both the younger and older age groups are shown in Tables 1 and 2. The results are for the right hemisphere as there was no significant difference between hemispheres for the same test condition.

There was a significant increase in the latency of the P2 component on eye closure, the mean increase being around 12.50 ms for both the older and younger group. These findings were significant, by means of a paired t-test, at the $P < 0.01$ level. There was no such significant increase in the latency of the P1 component in the older group. It should be noted that whereas for all 10 older subjects a readily identifiable P2 component was recordable from each eye only 5 subjects showed a recordable P1. The effect upon the amplitude of the components was more variable for both P1 and P2 and there was no significant difference in amplitude for either component.

Table 1. The group averaged eye open and eye closed data for the older age group

	Normal group		
	Eye open (SD)	Eye closed (SD)	Sign level
Latency			
RE P1	73.69 (5.24)	69.53 (8.60)	Not sign
N2	87.23 (11.84)	89.20 (5.99)	Not sign
P2	120.83 (8.49)	133.73 (16.29)	$P < 0.005$
LE P1	69.55 (5.87)	72.10 (5.01)	Not sign
N2	85.90 (9.29)	87.48 (8.47)	Not sign
P2	120.56 (10.57)	132.53 (18.71)	$P < 0.01$
Amplitude			
RE N1-P1	4.55 (2.97)	3.10 (1.73)	Not sign
N2-P2	9.48 (5.03)	8.65 (4.22)	Not sign
N1-P1	3.57 (2.91)	3.45 (1.72)	Not sign
N2-P2	11.40 (5.59)	8.83 (3.94)	Not sign

Table 2. The group averaged eye open and eye closed data for the younger age group

	Normal group		
	Eye open (SD)	Eye closed (SD)	Sign level
Latency			
RE N2	72.26 (13.22)	84.70 (11.46)	$P < 0.02$
P2	115.50 (8.69)	129.73 (10.34)	$P < 0.001$
LE N2	72.37 (14.2)	78.29 (15.59)	Not sign
P2	116.63 (6.98)	127.13 (10.49)	$P < 0.001$
Amplitude			
RE N2-P2	10.17 (5.09)	10.09 (5.09)	Not sign
LE N2-P2	12.00 (5.09)	9.46 (5.13)	Not sign

The results below are also for the right hemisphere as there was no significant difference between the hemispheres for the same test conditions except for one condition in the colour study which will be noted later. The statistical test applied throughout was the paired *t*-test.

The neutral density filter study

The group averaged results of the neutral density filter study are shown in Fig. 1. As previously stated the P2 latency when the eye was closed was significantly later at the $P < 0.001$ level compared to the baseline eye open state with no neutral density filter and there was no significant difference in amplitude of the N2-P2 component. The placing of neutral density filters in front of the photostimulator did not significantly alter the P2 latencies from those recorded with the eye in the open state without any reduction in intensity. In addition there was no significant difference in amplitude of the response recorded compared to the baseline amplitude until the neutral density filter had reached 3 log units when the reduction in amplitude was significant at the $P < 0.005$ level.

The attention study

The group averaged results of the four conditions of stimulation are given in Fig. 2. These results show a significant difference between the eye open and eye closed latencies of the P2 component ($P < 0.001$). When performing a mental task no significant effect on the P2 latencies either for the eye open or the eye closed

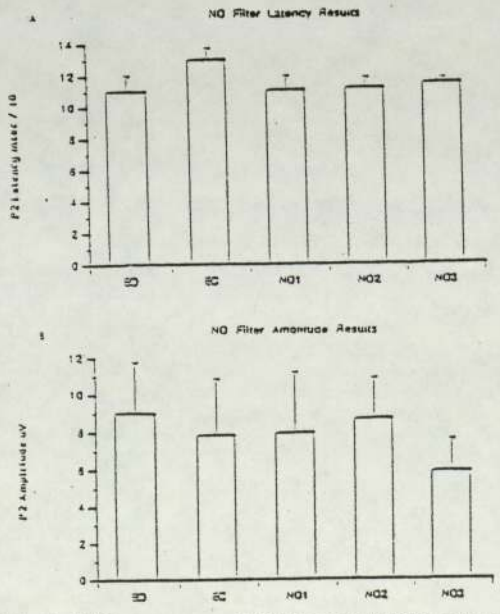

Fig. 1. (A) Group averaged P2 latency results for eye open (EO), eye closed (EC) and neutral density filters (ND). (B) Group averaged P2 amplitude results for the same study. Error bars represent ±1 S.D.

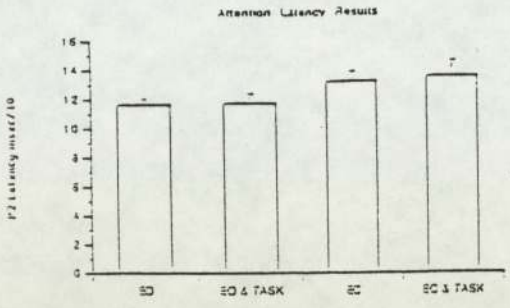

Fig. 2. Group averaged P2 latency results for eye open (EO) and eye closed (EC) situations with and without a mental task. Error bars represent +1 S.D.

states was found. The P2 latencies from the closed eye whilst performing a mental task were still significantly later than those recorded from the open eye ($P < 0.001$).

The ganzfeld study

The results again showed a significant increase in the latency of the P2 component with the eye closed compared to the baseline eye open recording ($P < 0.001$) Fig. 3. The latency of the P2 component to white light was not significantly altered by the use of a Ganzfeld form of stimulation. The latency of the P2 component to red light Ganzfeld stimulation was not significantly different from the latency of the P2 component recorded from the closed eye but was therefore, significantly later than the P2 latency of the open eye to white light ($P < 0.001$), both with and without the Ganzfeld effect.

The colour study

As for all the previous experiments there was a significant increase in the latency of the P2 component of the flash VER with the eye closed compared to the eye open situation but on this occasion the effect was only apparent for the right hemisphere ($P < 0.02$), the results for the left hemisphere did not reach significance ($P < 0.07$) Fig. 4. The latency of the P2 component recorded to either white or green light stimulation, from the open eye, showed no significant difference between the hemispheres. The results from the open eye to red light were significantly later than those obtained on white or gree light stimulation ($P < 0.006$) but were similar to those recorded from the closed eye to white light ($P < 0.295$).

DISCUSSION

The results showed that when a closed eye was stimulated by a flashing white light the P2 component of the VER recorded had a significantly longer latency compared to that recorded when the eye was open confirming the findings of Poole and Weaving (1987). There was no such effect on the P1 component. There was no significant effect upon the amplitude of responses recorded. The latencies and amplitudes recorded for the eye open states were in agreement with previously published normative results (Wright *et al.*, 1985). As a practical clinical point these findings indicate that eye closure has no significant effect on amplitude within the range of intensities used for stroboscopic stimulation.

There was no significant increase in the latency of the P2 component when neutral density filters were placed in front of the photostimulator. This finding is in agreement with Thorpe Davis *et al.* (1987). These results suggest therefore that the increase in P2 latency when the eye is closed is not due to the reduction in the luminance of the stimulus produced by the

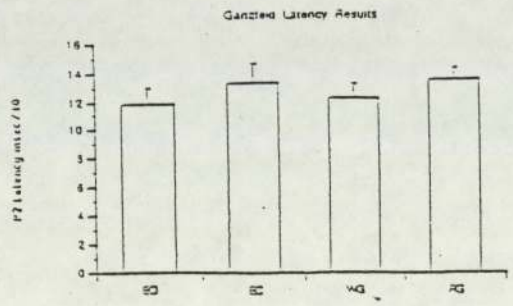

Fig. 3. Group averaged P2 latency results for eye open (EO), eye closed (EC), white Ganzfeld (WG) and red Ganzfeld (RG). Error bars represent +1 S.D.

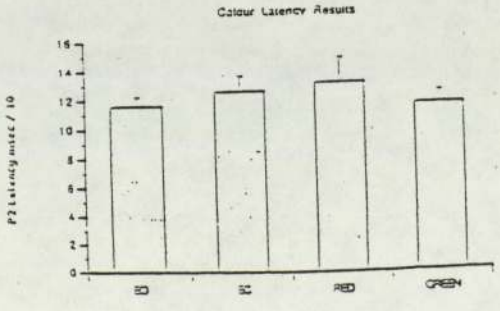

Fig. 4. Group averaged P2 latency results for eye open (EO) and eye closed (EC) to white light and for eye open to red and green light. Error bars represent +1 S.D.

closed lid. Whereas a significant reduction in the amplitude of the response compared to the eye open value resulted from the use of the 3 log unit neutral density filter, there was no significant difference between the eye open and eye closed amplitudes at normal photostimulator intensity. In order to control for discrepancies in intensity we studied four subjects at an additional intensity of 8 and one subject at intensity 16. The increase in latency on eye closure was approximately the same at all intensities. This would again suggest that the effect of eye closure on the P2 component is not one of luminance.

There are conflicting views as to the effect of a mental task such as mental arithmetic on the amount of alpha activity in the underlying EEG. These vary from attenuation of alpha activity in all or almost all subjects (Lorens and Darrow, 1962; Walter, 1959) to attenuation only in certain people (Mundy-Castle, 1957) to having no effect on the underlying alpha activity (Mulholland, 1969; Creutzfeldt *et al.*, 1969) or even increasing it (Kreitman and Shaw, 1965). If the increase in latency of the P2 component, when the eye was closed, was due to an increase in alpha activity in the underlying EEG, then recording the flash VER through a closed eye while the subject performed mental arithmetic tasks could alter the background alpha activity and reduce the effect of eye closure on the P2 latency. The performance of such a mental task had no effect on the P2 latency when the flash VER was recorded with the eye open or closed. This would suggest that the increase in P2 latency was unrelated to the amount of background alpha activity or that a mental arithmetic task did not cause attenuation of the underlying alpha activity. Alternatively there maybe more than one generator of alpha rhythm in the brain and perhaps different types of the alpha rhythm are affected differently by different attentional tasks. It would appear that if the P2 latency was being affected by alpha activity it was not the type of alpha activity which is attenuated by mental arithmetic.

The results from the Ganzfeld study suggest that the increase in the P2 latency was not related to the eyelid acting as a plain Ganzfeld but could be related to the closed eyelid acting as a red filter.

The Ganzfeld study had suggested and the colour study showed that the use of a red filter in front of the photostimulator did indeed produce a P2 latency that was significantly later than the eye open response but was similar to the eye closed response. This would suggest that the increase in P2 latency is due to the eyelid acting as a red filter. This finding is supported by the work of Crawford and Marc (1976) who measured the transmission spectra of the monkey eyelid *in vivo* and found that 15–25% of the transmission was of the longer wavelengths. Moseley and Fielder (1987) have attempted to replicate this work in humans and achieved similar results. Previous studies using red as the stimulus wavelength have either shown no effect upon the P2 latency of the response recorded (Siegfried, 1970; Paulus *et al.*, 1984) or that the P2 component to red stimulation was recorded earlier than for blue or green stimulation (White *et al.*, 1977). Siegfried's results (1970) were, however, obtained from two subjects and it is known that the flash response varies widely within the normal population (Harding, 1982). Paulus *et al.* (1984) used a LED stimulator, with a white surround, to generate different wavelengths of equal brightness. Although showing no change of the P2 response they did obtain a change in the N2 component. White *et al.* (1977) using a stroboscope with Wratten filters obtained an earlier P2 response on red stimulation than with the blue or the green. However, they do not state exact subject numbers and most of the data presented is from one subject. Comparison of previous studies is made difficult by the use of different stimulus conditions. A number of studies used Maxwellian view, patterned flash stimuli, varying backgrounds or different reference sites whereas in this study we maintained our standard clinical set up (Harding, 1974).

It should be noted that the P1 latency does not increase significantly on eye closure in contrast to the P2 component and this would suggest that the generators of the P1 and P2 components differ.

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ABSTRACT OF PAPER PRESENTED AT THE SOCIETY OF EXPERIMENTAL OPTOMETRY 1987 .

Ophthal. Physiol. Opt. 8: 106. 1988.

The Effect of Eye Closure Upon the Flash Visual Evoked Response

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The effect of eye closure upon the flash visual evoked response (VER) was studied. Two groups (mean ages of 52.2 and 22.1 years) had flash VERs recorded in both eye open and closed situations. With eye closure the latency of the P2 component was significantly increased compared with the eye open state for both groups, the mean increase being 12.95 and 13.33 ms respectively for the older and younger age groups. There was no significant increase in the latency of the P1 component where recordable or upon the amplitude of either the P1 or P2 component.

Whether the effect of eye closure was due to the eyelids reducing the intensity of the flash or acting as a Ganzfeld was tested. The stimulus intensity was reduced by placing neutral density filters in front of the photostimulator. The P2 latencies of the VERs recorded were all significantly shorter than the latencies recorded with the eye closed.

The P2 latencies of the VERs recorded using a white Ganzfeld were significantly shorter than the latencies recorded with the eyes closed but not significantly different from the eye open latencies. The P2 latency of the VERs recorded when using a red Ganzfeld, however, were not significantly different from the eye closed results but were not significantly longer than the eye open results.

These results suggest that the P1 and P2 components are generated at different sites as only P2 is affected by closing the eyes. This work also suggests that the increase in the P2 latency is not related to reduced stimulus intensity but could be related to the closed lid acting as a red filter but not as a plain Ganzfeld.

Further work is proposed to investigate the effect of colour by using luminance matched filters.

ABSTRACT OF PAPER PRESENTED AT THE EEG SOCIETY MEETING, APRIL 1988.

Electroenceph. clin. Neurophysiol. (In Press).

THE EFFECT OF DIFFERENT REFERENCE SITES ON THE INCIDENCE AND AMPLITUDE OF THE P1 COMPONENT OF THE FLASH VER

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It is common practice to record the flash VER referred to either the midfrontal or central electrodes. A balanced non-cephalic reference was used to investigate the suitability of these electrode positions as reference sites for flash VER recording. Thirty subjects were equally divided by age into three groups, a young group (mean 26 years), a middle group (mean 49.4 years) and an older group (mean 72.5 years). The P2 component of the flash VER was recorded consistently over the occipital region throughout the age range, as was a frontal negative component of similar latency (N120). The young age group only had this single negative component on frontal channels, whereas the middle age group showed a second earlier negative component at around 75 msec (N75). Neither of these groups had a recordable P1 component over the occipital region. The older group showed both P1 and P2 components over the occipital region and negative N75 and N120 components on the frontal channels.
This work suggests that the use of the midfrontal or central electrodes as the reference site for flash VER recording may produce an artificial P1 component in middle aged subjects and an artificial enhancement of the component in the elderly.

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